I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on December 16, 2009.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 AND UNDER 37 CFR 1.323
Docket No. MET.037CXT
Patent No. 7,563,774

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Paul D. van Poelje, Mark D. Erion, Toshihiko Fujiwara
Issued	:	July 21, 2009
Patent No.	:	7,563,774
Conf. No.	:	7049
For	:	Combination of FBPase Inhibitors and Antidiabetic Agents Useful for the Treatment of Diabetes

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)
UNDER 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 6, lines 60-61:	Page 10, line 3:
"-oxyalkyleneaamino-"	-- -oxyalkyleneamino- --

Column 7, line 5:

"include norbomyl"

Column 10, line 55:

"Kharnnei"

Patent Reads:

Column 26, line 7:

"all except H"

Column 26, line 26:

"OR^3 and"

Patent Reads:

Column 26, line 63:

"R^{16} is $-(CR^{12}R^{13})_nC(O)-R^{14}$,"

Patent Reads:

Column 27, line 60:

"OR^3 and"

Patent Reads:

Column 36, line 50:

"amnidine"

Column 36, line 52:

"C_2-C_5 alkeniyl"

Column 37, line 10:

"the R attached"

Page 10, line 11:

--include norbornyl--

Page 16, line 3:

--Khamnei--

Application Should Read:

Page 36, line 7:

--all except —H--

Page 36, line 23:

-- —OR^3 and--

Application Reads:

Page 37, line 13:

--R^{16} is $-(CR^{12}R^{13})_n$-C(O)-R^{14}--

Application Should Read:

Page 39, line 8:

-- —OR^3 and--

Application Reads:

Page 53, line 12:

--amidine--

Page 53, line 13:

--C_2-C_5 alkenyl--

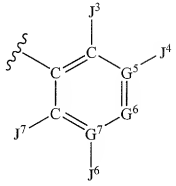
Page 54, line 17:

--the R^1 attached--

Column 43, line 19:	Page 63, line 28:
"prodrugs and salts"	--salts or prodrugs--
Column 46, line 15:	Page 68, line 7:
"form a bidendate"	--form a bidentate--
Column 49, line 33:	Page 72, line 11:
"A, E, and L are independently selected"	--A, E, and L are selected--
Column 51, line 27:	Page 75, line 22:
"bidendate"	--bidentate--
Patent Reads:	**Application Should Read:**
Column 51, line 64:	Page 76, line 18:
"C1-C5 alkyl or"	--C_1-C_5 alkyl, or--
Patent Reads:	**Application Reads:**
Column 54, line 30:	Page 79, line 14:
"-alkylthio-alkyl-, -alkyl-thio-,"	-- -alkylthioalkyl-, -alkylthio-,--
Column 58, line 15:	Page 85, line 15:
"are not $-NR^6$;"	--are not $-NR^6-$;--
Column 59, line 20:	Page 87, line 1:
"Y is $-NR^6$,"	--Y is $-NR^6-$,--
Column 62, line 41:	Page 92, line 5:
"from –H, or together"	--from –H, alkyl, or together--
Column 62, line 42:	Page 92, line 5:
"R^4 from a"	--R^4 form a--

Column 64, lines 20-26:

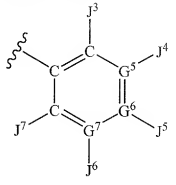
“ VII-6



”

Page 94, lines 15-18:

-- VII-6



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Column 64, line 42:

“alkenyl, alkylenearyl”

Page 95, lines 7-8:

--alkenyl, alkynyl, alkylenearyl--

Column 66, line 22:

“R" is”

Page 98, line 3:

--R^{11} is--

Column 68, line 48:

“—$OCOR^3$, —$OCOR^3$”

Page 101, line 14:

-- —$OCOR^3$, —OCO_2R^3--

Column 69, line 51:

“together with R^6”

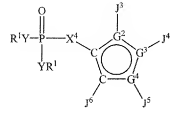
Page 103, line 11:

--together with R^{16}--

Column 70, line 40:

“thereof.

VII-1



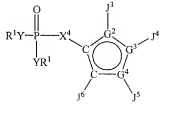
”

Page 104, lines 17-18:

--thereof.

In one aspect of the present invention compounds of formula VII-1 are envisioned.

VII-1



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Column 70, line 51:

"In one aspect"

Column 70, line 67:

"formula VII-1"

Column 72, line 11:

"—OC_2R^3"

Column 73, line 23:

"$CHR^2OC(S)OR^3$"

Column 73, line 27:

"SCO_2R^3"

Column 73, lines 45-46:

"—CH(aryl)OH, **13** $CH(CH=CR^2{}_2)OH$"

Column 73, line 56:

"and **13** $OC(O)SR^3$"

Column 74, lines 65-66:

"**13** $CHR^2OC(O)SR^3$"

Column 75, line 25:

"—$CHR_2NHaryl$"

Column 75, lines 33-34:

"**13** OCO_2R^3"

Column 75, line 65:

"—$C(R^4)_2C(O)^3$, or"

Page 104, line 19:

--In another aspect--

Page 105, line 1:

--formula VII-1-A--

Page 106, line 17:

-- —OCO_2R^3--

Page 108, lines 16-17:

-- —$CHR^2OC(S)OR^3$--

Page 108, line 19:

-- —SCO_2R^3--

Page 109, line 8:

-- —CH(aryl)OH, —$CH(CH=CR^2{}_2)OH$--

Page 109, line 15:

--and —$OC(O)SR^3$--

Page 111, line 9:

-- —$CHR^2OC(O)SR^3$--

Page 112, line 3:

-- —$CH_2NHaryl$--

Page 112, line 9:

-- —OCO_2R^3--

Page 112, line 28:

-- —$C(R^4)_2C(O)OR^3$, or--

Patent Reads:	**Application Should Read:**
Column 76, lines 20-21:	Page 113, line 8:
"aspect are compounds are such"	--aspect are compounds such--
Patent Reads:	**Application Reads:**
Column 85, lines 63-64:	Page 131, line 12:
"7 one Y is $-NR^6-$, and the other YR^1 is $NR^{15}R^{16}$, and R^{15} is not H"	--7 one Y is $-NR^6-$, and the other YR^1 is $—NR^{15}R^{16}$, and R^{15} is not H--
Column 85, lines 65-66:	Page 131, lines 13-14:
"8 one Y is $-NR^6-$, and the other YR^1 is $NR^{15}R^{16}$,"	--8 one Y is $-NR^6-$, and the other YR^1 is $—NR^{15}R^{16}$,--
Column 86, lines 14-16:	Page 131, lines 18-19:
"10 one Y is $-NR^6-$, and the other YR^1 is $NR^{15}R^{16}$, and R^{16} is, where $-NR^{15}R^{16}$ is a cylic amine"	--10 one Y is $-NR^6-$, and the other YR^1 is $—NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is a cylic amine--
Column 86, lines 17-19:	Page 131, lines 20-21:
"11 one Y is $-NR^6-$, and the other YR^1 is $NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is a selected from a group of morpholinyl and pyrrolidinyl"	--11 one Y is $-NR^6-$, and the other YR^1 is $—NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is selected from the group of morpholinyl and pyrrolidinyl--
Column 86, lines 19-20:	Page 131, lines 22-23:
"12 one Y is $-NR^6-$, and the other YR^1 is $NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is a $-(CR^{12}R^{13})_n—C(O)R^{14}$,"	--12 one Y is $-NR^6-$, and the other YR^1 is $—NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is $-(CR^{12}R^{13})_n—C(O)R^{14}$--
Column 86, line 44:	Page 132, line 14:
"$OCOR^3$,"	-- $—OCOR^3$,--

Column 87, line 15:

"—OR^2, R^2"

Patent Reads:

Page 133, line 16:

-- —OR^2, —R^2--

Application Should Read:

Column 96, lines 53-54:

"groups are O—"

Page 146, line 7:

--groups are —O— --

Column 101, line 61:

"Bis-[4-(1-triazolophenyl) esters;"

Page 153, line 25:

--Bis-[4-(1-triazolophenyl)] esters;--

Patent Reads:

Column 104, line 4:

"Bis-(phenyloxycarbonyloxyrnethyl) esters;"

Application Reads:

Page 156, line 17:

--Bis-(phenyloxycarbonyloxymethyl) esters;--

Column 105, line 9:

"of formula"

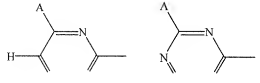
Page 157, lines 31-32:

--of formula I-A.--

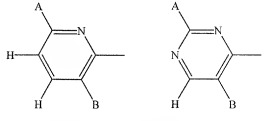
Column 105, Group 2:

Page 158, line 10:

" 3 4 "



-- 3 4 --



Patent Reads:

Column 106, line 36:

"5. —NH—$CH(CH(CH_3)_2)$—$C(O)R^{14}$"

Application Should Read:

Page 159, Group 1: 5.:

--5. —NH—$CH(CH(CH_3)_2)$—$C(O)R^{14}$--

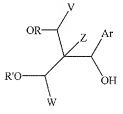
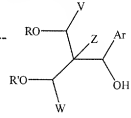
Column 106, line 37:

"6. —NH—$CH(CH_2(CH(CH_3)_2))$—$C(O)R^{14}$"

Page 159, Group 1: 6.:

--6. —NH—$CH(CH_2(CH(CH_3)_2))$—$C(O)R^{14}$--

Patent Reads:	**Application Reads:**
Column 107, line 1:	Page 159, Group 2: 4.:
"4. —NH—$CH(CH_2CoNH_2)$—$C(O)R^{14}$,"	--4. —NH—$CH(CH_2CONH_2)$—$C(O)R^{14}$--
Column 108, line 55:	Page 161, line 19:
"4. —N—$C(CH_3)_2CH_2$—$C(O)R^{14}$,"	--4. —NH—$C(CH_3)_2CH_2$—$C(O)R^{14}$--
Patent Reads:	**Application Should Read:**
Column 108, line 56:	Page 161, line 20:
"5. —N—$CH(CH(CH_3)_2)$—$C(O)R^{14}$,"	--5. —N—$CH(CH(CH_3)_2)$—$C(O)R^{14}$--
Column 108, line 57:	Page 162, line 1:
"6. —NH—$CH(CH_2(CH(CH_3)_2))$—$C(O)R^{14}$,"	--6. —NH—$CH(CH_2(CH(CH_3)_2))$—$C(O)R^{14}$--
Column 149, lines 33-34:	Page 207, lines 15-16:
"early stages diabetes"	--early stage diabetes--
Patent Reads:	**Application Reads:**
Column 150, line 15:	Page 208, line 20:
"Insulin/Insulin Analozues"	--Insulin/Insulin Analogues--
Column 152, line 60:	Page 212, line 21:
"Wiemsperger"	--Wiernsperger--
Column 158, line 56:	Page 222, line 4:
"CP-9971 1"	--CP-99711--
Column 160, line 46:	Page 225, line 1:
"Foley T E"	--Foley J E--

Patent Reads:	**Application Should Read:**
Column 170, line 32:	Page 238, line 3:
"oxidation of one the"	--oxidation of one of the--
Patent Reads:	**Application Reads:**
Columns 171-172, bottom center figure:	Page 238, bottom right figure:
"  "	--  --
Column 174, line 33:	Page 243, line 7:
"alkylarninocarbonyl"	--alkylaminocarbonyl--
Column 177, line 32:	Page 247, line 22:
"(Dom et al,"	--(Dorn et al,--
Column 179, line 63:	Page 251, line 11:
"synthesis of f tiran"	--synthesis of furan--
Column 181, line 34:	Page 254, line 17:
"wherein G=S"	--wherein G"=S--
Patent Reads:	**Application Should Read:**
Column 182, line 3:	Page 255, line 2:
"can made in"	--can be made in--
Column 182, line 36:	Page 255, lines 24-25:
"reactions in presence of"	--reactions in the presence of--

Column 186, lines 9-10:	Page 259, line 30:
"are each optionally is a carboxamido"	--are each optionally a carboxamido--
Column 186, lines 21-22:	Page 260, line 7:
"are each optionally is an"	--are each optionally an--
Patent Reads:	**Application Reads:**
Column 192, lines 17-18:	Page 268, line 12:
"(1.1 n unole)"	--(1.1 mmole)--
Column 194, line 36:	Page 271, line 28:
"N: 5.5"	--N: 5.53--
Column 195, lines 34-35:	Page 273, line 18:
"(3.27) 2-Amino-5-cyclopropyl-4-[2-(5-phosphono)fi aranyl]thiazole."	--(3.27) 2-Amino-5-cyclopropyl-4-[2-(5-phosphono)furanyl]thiazole.--
Column 195, line 60:	Page 274, line 5:
"(3.33) ^{2}-Amino-"	--(3.33) 2-Amino- --
Column 196, line 1:	Page 274, line 11:
"(3.35) ^{2}-Amino-"	--(3.35) 2-Amino- --
Column 196, line 5:	Page 274, line 14:
"(3.36) ^{2}-Amino-"	--(3.36) 2-Amino- --
Column 196, line 20:	Page 274, line 25:
"(3.40) ^{2}-Amino-"	--(3.40) 2-Amino- --
Column 196, line 27:	Page 274, line 31:
"(3.42) ^{2}-Methyl-"	--(3.42) 2-Methyl- --

Column 196, line 28:	Page 275, line 1:
"$C_{11}H_{12}NO_4PS+0.3$"	--$C_{11}H_{12}NO_4PS+0.3$--
Column 197, line 48:	Page 276, line 31:
"(3.67) ^{2}-Amino-"	--(3.67) 2-Amino- --
Column 199, line 50:	Page 280, line 1:
"(3 m mole)"	--(3 mmole)--
Column 200, line 6:	Page 280, lines 16-17:
"N: 10.21."	--N: 11.18.--
Column 200, lines 45-46:	Page 281, line 14:
"(6.2) 2-Methyl-5-isopropyl-4-[2-(5-phosphorodiamido)f tiranyl]thiazole"	--(6.2) 2-Methyl-5-isopropyl-4-[2-(5-phosphorodiamido)furanyl]thiazole--
Column 201, lines 47-49:	Page 283, lines 3-4:
"2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1-methoxycarbonyl)ethyl)phosphona mnido]-furanyl}thiazole"	--2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1-methoxycarbonyl)ethyl)phosphonamido]-furanyl}thiazole--
Column 203, line 24:	Page 285, lines 23-24:
"$C_{21}H_{24}N_3O_5PS+0.2$"	--$C_{21}H_{24}N_{30}O_5PS+0.2$--
Column 203, lines 35-37:	Page 286, lines 1-2:
"(6.35) 2-amino-5-isobutyl-4-{2-[5-(4,5-benzo-1-oxo-1-phospha-2-oxa-6-6-aza)cyclohexan-1-yl]fi aranyl}thiazole."	--(6.35) 2-amino-5-isobutyl-4-{2-[5-(4,5-benzo-1-oxo-1-phospha-2-oxa-6-aza)cyclohexan-1-yl]furanyl}thiazole.--
Column 203, line 50:	Page 287, line 7:
"A solution of AlC_{13}"	--A solution of $AlCl_3$--

Column 204, line 1:

"with CH_2C_{12}"

Patent Reads:

Page 287, line 19:

--with CH_2Cl_2--

Application Should Read:

Column 207, lines 24-25:

"C: 52.26; 7.06; 10.60. Found: C: 52.21; 6.93; 10.62."

Page 292, line 24:

--C: 52.26; H: 7.06; N: 10.60. Found: C: 52.21; H: 6.93; N: 10.62.--

Patent Reads:

Column 207, line 32:

"C_{35} H_{45} N_4 $_{O6}$ P S+0.5"

Application Reads:

Page 292, line 29:

--C_{35} H_{45} N_4 O_6 P S+0.5--

Patent Reads:

Column 207, line 47:

"P S3: C:"

Application Should Read:

Page 293, line 8:

--P S_3: C:--

Column 207, line 56:

"H: 6.97; H: 7.90. Found: C: 62.85; h 7.06, 7.81."

Page 293, line 15:

--H: 6.97; N: 7.90. Found: C: 62.85; H: 7.06, N: 7.81.--

Column 208, lines 2-3:

"H: 8.42. Found: C: 59.88; H: 6.28; H: 8.32."

Page 293, line 24:

--N: 8.42. Found: C: 59.88; H: 6.28; N: 8.32.--

Column 208, line 8:

"H: 8.98."

Page 293, line 27:

--N: 8.98.--

Patent Reads:	**Application Reads:**
Column 208, line 39:	Page 294, line 18:
"bis-phosphoroarnidate"	--bis-phosphoroamidate--
Column 209, line 35:	Page 296, lines 1-2:
"N_3-methyl-2-iodobenzene-1-sulfonamide"	--N^1-methyl-2-iodobenzene-1-sulfonamide--
Column 209, lines 40-42:	Page 296, lines 4-6:
"N^1-(4-5 chlorobenzyl)-2-iodobenzamide (for 13.14); Nl-(4-chlorophenethyl)-2-iodobenzamide (for 13.15); N1-benzyl-2-iodobenzene-1-sulfonamide"	--N^1-(4-chlorobenzyl)-2-iodobenzamide (for 13.14); N^1-(4-chlorophenethyl)-2-iodobenzamide (for 13.15); N^1-benzyl-2-iodobenzene-1-sulfonamide--
Column 209, line 51:	Page 296, line 12:
"N1-(2,4-difluorophenyl)-2-iodobenzamide"	--N^1-(2,4-difluorophenyl)-2-iodobenzamide--
Column 209, line 55:	Page 296, lines 14-15:
"(for 15 13.31);"	--(for 13.31);--
Patent Reads:	**Application Should Read:**
Column 209, lines 63-64:	Page 296, lines 20-21:
"N1-(4-iodophenyl)-2-tetrahydro-1H-pyrrol-1-ylacetamide"	--N^1-(4-iodophenyl)-2-tetrahydro-1H-pyrrol-1-ylacetamide--
Patent Reads:	**Application Reads:**
Column 210, line 28:	Page 297, line 8:
"(1 m mol)"	--(1 mmol)--
Column 213, line 42:	Page 301, line 12:
"2 MM"	--2 mM--

Column 214, line 47:	Page 302, line 32:
"Vervoom"	--Vervoorn--
Column 216, line 28:	Page 305, line 12:
"5-bromo-1-μD-ribofuranosyl-imidazole-carboxamide"	--5-bromo-1-βD-ribofuranosyl-imidazole-carboxamide--
Patent Reads:	**Application Should Read:**
Column 220, line 49:	Page 311, line 7:
"though"	--through--
Column 224, line 25:	Page 315, line 21:
"4 treatments groups"	--4 treatment groups--
Column 244, line 50:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 120, renumbered as claim 7):
"R1 is"	--R^1 is--
Column 244, line 53:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 121, renumbered as claim 8):
"B" is a C^1-C^6 alkyl"	--B" is a C_1-C_6 alkyl--
Column 244, lines 60-61:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 123, renumbered as claim 10):
"a C1-C6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; and YR1 is OH."	--a C_1-C_6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; and YR^1 is OH.--

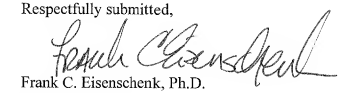
Column 244, lines 63-64:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 124, renumbered as claim 11):
"C1-C6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R1 is"	--C_1-C_6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is--
Column 245, line 2:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 126, renumbered as claim 13):
"and R1 is"	--and R^1 is--
Column 245, line 7:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 127, renumbered as claim 14):
"B" is a C1-C6"	--B" is a C_1-C_6--
Column 245, line 14:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 129, renumbered as claim 16):
"is a C1-C6"	--is a C_1-C_6--
Column 245, lines 16-17:	Election Under 35 U.S.C. § 121 dated April 24, 2006 (original claim 129, renumbered as claim 16):
"and R1 is"	--and R^1 is--.

A true and correct copy of pages 10, 16, 37, 53, 54, 63, 68, 72, 75, 79, 85, 87, 92, 94, 95, 98, 101, 103-106, 108, 109, 111, 112, 131-133, 156-159, 161, 208, 212, 222, 225, 238, 243, 247, 251, 254, 268, 271, 273-276, 280-281, 283, 285-287, 292, 294, 296, 297, 301, 302, and 305 of the specification as filed which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

The fee of $100.00 was paid at the time this Request was filed. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



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Attachments: Copy of pages 10, 16, 37, 53, 54, 63, 68, 72, 75, 79, 85, 87, 92, 94, 95, 98, 101, 103-106, 108, 109, 111, 112, 131-133, 156-159, 161, 208, 212, 222, 225, 238, 243, 247, 251, 254, 268, 271, 273-276, 280-281, 283, 285-287, 292, 294, 296, 297, 301, 302, and 305 of the specification

The term "-oxyalkylamino-" refers to -O-alk-NR-, where "alk" is an alkylene group and R is H or alkyl. Thus "-oxyalkylamino-" is synonymous with "-oxyalkyleneamino-."

The term "-alkylcarboxyalkyl-" refers to the group -alk-C(O)-O-alk- where each "alk" is independently an alkylene group.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched chain and cyclic groups. Alkyl groups may be optionally substituted. Suitable alkyl groups include, for example, those containing 1 to about 20 carbon atoms (e.g., methyl, isopropyl, and cyclopropyl).

The term "cyclic alkyl" or "cycloalkyl" refers to alkyl groups that are cyclic groups of 3 to 10 atoms, more preferably 3 to 6 atoms. Suitable cyclic groups include norbornyl and cyclopropyl. Such groups may be substituted.

The term "heterocyclic" and "heterocyclic alkyl" refer to cyclic groups of 3 to 10 atoms, more preferably 3 to 6 atoms, containing at least one heteroatom, preferably 1 to 3 heteroatoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Heterocyclic groups may be attached through a nitrogen or through a carbon atom in the ring. Suitable heterocyclic groups include pyrrolidinyl, morpholino, morpholinoethyl, and pyridyl.

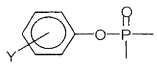
The term "phosphono" refers to $-PO_3R_2$, where R is selected from -H, alkyl, aryl, aralkyl, and alicyclic.

The term "sulphonyl" or "sulfonyl" refers to $-S(O)_2OR$, where R is selected from H, alkyl, aryl, aralkyl, and alicyclic.

The term "alkenyl" refers to unsaturated groups which contain at least one carbon-carbon double bond and includes straight-chain, branched-chain and cyclic groups. Alkenyl groups may be optionally substituted. Suitable alkenyl groups include allyl. "1-alkenyl" refers to alkenyl groups where the double bond is between the first and second carbon atom. If the 1-alkenyl group is attached to another group, *e.g.*, it is a W substituent attached to the cyclic phosph(oramid)ate, it is attached at the first carbon.

The term "alkynyl" refers to unsaturated groups which contain at least one carbon-carbon triple bond and includes straight-chain, branched-chain and cyclic groups. Alkynyl groups may be optionally substituted. Suitable alkynyl groups include ethynyl. "1-alkynyl" refers to alkynyl groups where the triple bond is between the first and second

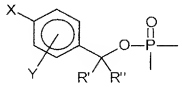
generated the parent phosphonic acid in studies conducted in animals and in man (Formula C). Another approach has been described where Y is a carboxylic ester ortho to the phosphate. Khamnei and Torrence, J. Med. Chem.; 39:4109-4115 (1996).



Formula C

wherein Y is H, alkyl, aryl, alkylaryl, alkoxy, acyloxy, halogen, amino, alkoxycarbonyl, hydroxy, cyano, or alicyclic.

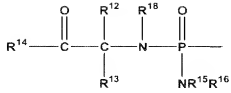
[5] Benzyl esters have also been reported to generate the parent phosphonic acid. In some cases, using substituents at the para-position can accelerate the hydrolysis. Benzyl analogs with 4-acyloxy or 4-alkyloxy group [Formula D, X = H, OR or O(CO)R or O(CO)OR] can generate the 4-hydroxy compound more readily through the action of enzymes, *e.g.*, oxidases, esterases, etc. Examples of this class of prodrugs are described in Mitchell et al., J. Chem. Soc. Perkin Trans. I 2345 (1992); Brook, et al. WO 91/19721.



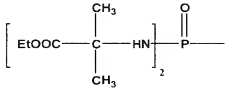
Formula D

wherein X and Y are independently H, alkyl, aryl, alkylaryl, alkoxy, acyloxy, hydroxy, cyano, nitro, perhaloalkyl, halo, or alkyloxycarbonyl; and R' and R'' are independently H, alkyl, aryl, alkylaryl, halogen, and alicyclic.

[6] Thio-containing phosphonate proesters have been described that are useful in the delivery of FBPase inhibitors to hepatocytes. These proesters contain a protected thioethyl moiety as shown in formula E. One or more of the oxygens of the phosphonate can be esterified. Since the mechanism that results in de-esterification requires the



is selected from the group of:



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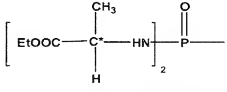


wherein C* has S stereochemistry;

R^{18} and R^{15} are selected from H, and methyl;

each R^{12} and R^{13} is independently selected from -H, methyl, i-propyl, i-butyl, and benzyl, or together R^{12} and R^{13} are connected via 2-5 carbon atoms to form a cycloalkyl group;

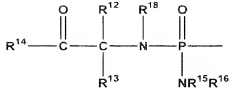
n is 1;

R^{14} is $-OR^{17}$;

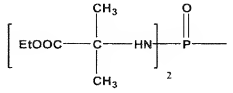
R^{16} is $-(CR^{12}R^{13})_n-C(O)-R^{14}$; and

R^{17} is selected from methyl, ethyl, propyl, phenyl, and benzyl.

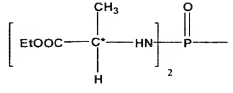
Also particularly preferred are such compounds wherein R^5 is selected from:



is selected from

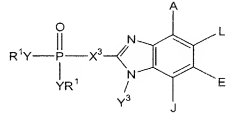


and



wherein C* has S stereochemistry.

In one aspect, preferred are compounds of formula III:



III

wherein:

A, E, and L are selected from -$NR^8{}_2$, -NO_2, -H, -OR^7, -SR^7, -$C(O)NR^4{}_2$, halo, -COR^{11}, -SO_2R^3, guanidine, amidine, -$NHSO_2R^{25}$, -$SO_2NR^4{}_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic

group, or together E and J form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y^3 forms a cyclic group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X^3 is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2_2$;

Y^3 is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, aryloxyalkyl, alkoxyalkyl, $-C(O)R^3$, $-S(O)_2R^3$, $-C(O)-R^{11}$, $-CONHR^3$, $-NR^2_2$, and $-OR^3$, all except H are optionally substituted;

Y is independently selected from -O- and $-NR^6$, with the provisos that:

when Y is -O-, the R^1 attached to -O- is independently selected from -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or a thiocarbonate, optionally substituted -arylalkyl, $-C(R^2)_2OC(O)NR^2_2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy;

when Y is $-NR^6$-, the R^1 attached to $-NR^6$- is independently selected from -H, $-[C(R^2)_2]_q-COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q-C(O)SR$, and -cycloalkylene-$COOR^3$, where q is 1 or 2;

when only one Y is -O-, which -O- is not part of a cyclic group containing the other Y, the other Y is $-N(R^{18})-(CR^{12}R^{13})-C(O)-R^{14}$; and

when Y is independently selected from -O- and $-NR^6$, and form a cyclic group, or together, R^1 and R^1 form :

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from the group of -H, alkylene, -alkylenearyl and aryl, or together R^4 and R^4 are connected via 2-6 atoms, optionally including one heteroatom selected from the group of O, N, and S;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13}, together, are connected via 2-6 carbon atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2R^{20}$;

R^{15} is selected from -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or, when R^{14} is $-N(R^{17})_2$, together, both R^{17}s are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{20} is selected from the group of –H, lower R^3, and –C(O)-lower R^3;

and pharmaceutically acceptable salts or prodrugs thereof.

In another aspect of the invention are compounds of formula I and formula IA, wherein M is:

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-(CO)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together both R^8s form a bidentate alkyl;

R^9 is selected from alkyl, aralkyl, and alicyclic;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl; and

R^{11} is selected from alkyl, aryl, $-NR_2^2$, and $-OR^2$;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13}, together, are connected via 2-6 carbon atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2R^{20}$;

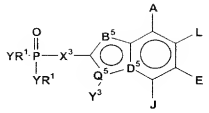
R^{15} is selected from -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or, when R^{14} is $-N(R^{17})_2$, together, both R^{17}s are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{20} is selected from the group of –H, lower R^3, and –C(O)-lower R^3;

and pharmaceutically acceptable prodrugs and salts thereof.



IV

wherein:

B^5 is selected from -NH-, -N= and -CH=;

D^5 is selected from $-\overset{|}{C}=$ and $-\overset{|}{N}-$

Q^5 is selected from –C= and –N-;

with the proviso that:

when B^5 is -NH- then Q^5 is -C= and D^5 is $-\overset{|}{C}=$,

when B^5 is -CH= then Q^5 is -N- and D^5 is $-\overset{|}{C}=$, and

when B^5 is -N=, then D^5 is $-\overset{|}{N}-$ and Q^5 is -C=;

A, E, and L are selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-COR^{11}$, $-SO_2R^3$, guanidino, amidino, $-NHSO_2R^{25}$, $-SO_2NR^4_2$, -CN, sulfoxide, perhaloacyl, perhaloalkyl, perhaloalkoxy, C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, and lower alicyclic, or together A and L form a cyclic group, or together L and E form a cyclic group, or together E and J form a cyclic group selected from the group of aryl, cyclic alkyl, and heterocyclic;

J is selected from $-NR^8_2$, $-NO_2$, -H, $-OR^7$, $-SR^7$, $-C(O)NR^4_2$, halo, $-C(O)R^{11}$, -CN, sulfonyl, sulfoxide, perhaloalkyl, hydroxyalkyl, perhaloalkoxy, alkyl, haloalkyl, aminoalkyl, alkenyl, alkynyl, alicyclic, aryl, and aralkyl, or together with Y^3 forms a cyclic group selected from the group of aryl, cyclic alkyl and heterocyclic alkyl;

X^3 is selected from -alkyl(hydroxy)-, -alkyl-, -alkynyl-, -aryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alicyclic-, -aralkyl-, -alkylaryl-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W" are not all –H;

R^2 is selected from R^3 and –H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

R^{25} is selected from lower alkyl, lower aryl, lower aralkyl, and lower alicyclic;

R^7 is independently selected from -H, lower alkyl, lower alicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together they form a bidentate alkyl;

R^9 is selected from alkyl, aralkyl, and alicyclic;

R^{10} is selected from -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from alkyl, aryl, $-NR_2^2$ and $-OR^2$;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13}, together, are connected via 2-6

each B and D are independently selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, aralkyl, alkoxyalkyl, $-C(O)R^{11}$, $-C(O)SR^3$, $-SO_2R^{11}$, $-S(O)R^3$, -CN, $-NR^9{}_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, $-NO_2$, and null, all except -H, -CN, perhaloalkyl, $-NO_2$, and halo are optionally substituted;

E is selected from -H, alkyl, alkenyl, alkynyl, aryl, alicyclic, alkoxyalkyl, $-C(O)OR^3$, $-CONR^4{}_2$, -CN, $-NR^9{}_2$, $-NO_2$, $-OR^3$, $-SR^3$, perhaloalkyl, halo, and null, all except -H, -CN, perhaloalkyl, and halo are optionally substituted;

J is selected from -H and null;

X is an optionally substituted linking group that links R^5 to the phosphorus atom via 2-4 atoms, including 0-1 heteroatoms selected from N, O, and S, except that if X is urea or carbamate there is 2 heteroatoms, measured by the shortest path between R^5 and the phosphorus atom, and wherein the atom attached to the phosphorus is a carbon atom, and wherein X is selected from -alkyl(hydroxy)-, -alkynyl-, -heteroaryl-, -carbonylalkyl-, -1,1-dihaloalkyl-, -alkoxyalkyl-, -alkyloxy-, -alkylthioalkyl-, -alkylthio-, -alkylaminocarbonyl-, -alkylcarbonylamino-, -alkoxycarbonyl-, -carbonyloxyalkyl-, -alkoxycarbonylamino-, and -alkylaminocarbonylamino-, all optionally substituted; with the proviso that X is not substituted with $-COOR^2$, $-SO_3H$, or $-PO_3R^2{}_2$;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, and alkyl, or together R^4 and R^4 form a cyclic alkyl group;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from alkyl, aryl, $-NR^2{}_2$, and $-OR^2$;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13}, together, are connected via 2-6

aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D'' is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the proviso that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ; and

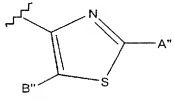
b) both Y groups are not $-NR^6-$;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from -H, and lower alkyl.

In one particularly preferred aspect of formula I where M is $–X-R^5$ and R^5 is



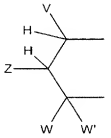
X is selected from methylenoxycarbonyl, and furan-2,5-diyl; at least one Y group is -O-; and pharmaceutically acceptable salts and prodrugs thereof. More preferred are such compounds wherein when Y is -O-, then R^1 attached to -O- is independently selected from -H, optionally substituted phenyl, $-CH_2OC(O)$-tBu, $-CH_2OC(O)Et$ and $-CH_2OC(O)$-iPr;

when Y is $-NR^6-$, then R^1 is attached to $-NR^6-$ independently selected from $-C(R^2)_2COOR^3$, $-C(R^4)_2COOR^3$, or

when Y is -O- or $-NR^6-$, and at least one Y is -O-, then together R^1 and R^1 are

or when Y is -NR^6-, then each R^1 is independently selected from -$C(R^2)_2C(O)OR^3$, and -$C(R^4)_2COOR^3$;

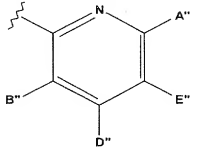
or when Y is independently selected from -O- and -NR^6-, then together R^1 and R^1 are



wherein

V selected from optionally substituted aryl and optionally substituted heteroaryl; and Z, W', and W are H. Also especially preferred are such compounds wherein B" is $-SCH_2CH_2CH_3$.

In another particularly preferred aspect of formula I where M is $-X-R^5$ and R^5 is



A" is $-NH_2$, E" and D" are -H, B" is n-propyl and cyclopropyl, X is furan-2,5-diyl and methyleneoxycarbonyl; at least one Y group is -O-; and pharmaceutically acceptable salts and prodrugs thereof. Especially preferred are such compounds wherein R^1 is selected from -H, optionally substituted phenyl -$CH_2OC(O)$-tBu, -$CH_2OC(O)$Et, and -$CH_2OC(O)$-iPr,

or when Y is -NR^6-, then each R^1 is independently selected from -$C(R^2)_2C(O)OR^3$, and -$C(R^4)_2COOR^3$;

or when either Y is independently selected from -O- and -NR^6-, and at least one Y is -O-, then together R^1 and R^1 are

with the proviso that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H;

R^2 is selected from R^3 and -H;

R^3 is selected from alkyl, aryl, alicyclic, and aralkyl;

each R^4 is independently selected from -H, alkyl, or together R^4 and R^4 form a cyclic alkyl;

R^6 is selected from -H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

each R^9 is independently selected from -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from alkyl, aryl, $-NR^2_2$, and $-OR^2$;

n is an integer from 1 to 3;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

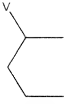
each R^{12} and each R^{13} is independently selected from H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13}, together, are connected via 2-6 carbon atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2R^{20}$;

R^{15} is selected from -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

R^{16} is selected from $-(CR^{12}R^{13})_n-C(O)-R^{14}$, -H, lower alkyl, lower aryl, and lower aralkyl, or, together, R^{15} and R^{16} are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;

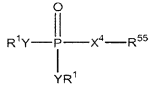
each R^{17} is independently selected from lower alkyl, lower aryl, and lower aralkyl, or, when R^{14} is $-N(R^{17})_2$, together, both R^{17}s are connected via 2-6 atoms to form a cyclic group, wherein the cyclic group optionally includes one heteroatom selected from O, N, and S;



and V is phenyl substituted with 1-3 halogens. Especially preferred are such 3-bromo-4-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, and 3,5-dichlorophenyl.

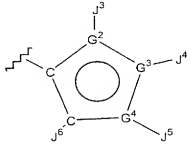
In another particularly preferred aspect, one Y is -O- and its corresponding R^1 is phenyl, or phenyl substituted with 1-2 substituents selected from -$NHC(O)CH_3$, -F, -Cl, -Br, -$C(O)OCH_2CH_3$, and -CH_3; while the other Y is -NR^6- and its corresponding R^1 is -$C(R^2)COOR^3$; each R^2 is independently selected from -H, -CH_3, and -CH_2CH_3. More preferred R^6 is -H, and R^1 attached to -NH- is -$CH(Me)CO_2Et$.

In another aspect of the invention are the following compounds of formula VII:

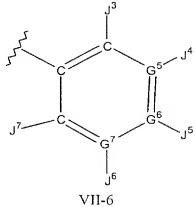


VII

wherein R^{55} is selected from the group of:



and



VII-5 VII-6

wherein:

G^2 is selected from the group of C, O, and S;

G^3 and G^4 are independently selected from the group of C, N, O, and S;

wherein a) not more than one of G^2, G^3, and G^4 is O, or S; b) when G^2 is O or S, not more than one of G^3 and G^4 is N; c) at least one of G^2, G^3, and G^4 is C; and d) G^2, G^3, and G^4 are not all C;

G^5, G^6 and G^7 are independently seleeted from the group of C and N, wherein no more than two of G^5, G^6 and G^7 are N;

J^3, J^4, J^5, J^6, and J^7 are independently selected from the group of -H, $-NR^4{}_2$, $-CONR^4{}_2$, $-CO_2R^3$, halo, $-S(O)_2NR^4{}_2$, $-S(O)R^3$, $-SO_2R^3$, alkyl, alkenyl, alkynyl, alkylcnearyl, perhaloalkyl, haloalkyl, aryl, heteroaryl, alkylene-OH, $-C(O)R^{11}$, $-OR^{11}$, -alkylene-$NR^4{}_2$, -alkylene-CN, -CN, $-C(S)NR^4{}_2$, $-OR^2$, $-SR^2$, $-N_3$, $-NO_2$, $-NHC(S)NR^4{}_2$, and $-NR^{21}COR^2$;

X^4 is selected from the group of:

i) a linking group having 2-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is seleeted from the group of –furanyl-, -thienyl-, -pyridyl-, -oxazolyl-, -imidazolyl-, -phenyl-, -pyrimidinyl-, –pyrazinyl-, and -alkynyl-, all of which may be optionally substituted; and

ii) a linking group having 3-4 atoms measured by the fewest number of atoms connecting the carbon of the aromatic ring and the phosphorus atom and is selected from the group of –alkylcarbonylamino-, -alkylaminocarbonyl-, -alkoxycarbonyl-, -alkoxy-, -alkylthio-, -alkylcarbonyloxy-, -alkyl-S(O)-, -alkyl-$S(O)_2$-, and –alkoxyalkyl-, all of which may be optionally substituted;

Y is independently seleeted from the group of -O-, and $-NR^6$-;

when Y is -O-, then R^1 attached to -O- is independently selected from the group of -H, alkyl, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-, $-C(R^2)_2OC(O)NR^2{}_2$, $-NR^2$-C(O)-R^3, $-C(R^2)_2$-$OC(O)R^3$, $-C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, -alkyl-S-S-alkylhydroxy, and -alkyl-S-S-S-alkylhydroxy,

when Y is $-NR^6$-, the R^1 attached to $-NR^6$- is independently selected from -H, $-[C(R^2)_2]_q$-$COOR^3$, $-C(R^4)_2COOR^3$, $-[C(R^2)_2]_q$-C(O)SR^3, and -cycloalkylene-$COOR^3$, where q is 1 or 2;

each R^9 is independently selected from the group of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group of alkyl, aryl, $-NR^2_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S;

R^{16} is selected from the group of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S;

each R^{17} is independently selected from the group of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

R^{19} is selected from the group of –H, and lower acyl;

R^{20} is selected from the group of –H, lower R^3, and –C(O)-(lower R^3);

R^{21} is selected from the group of –H and lower R^3;

n is an integer from 1 to 3;

with the provisos that:

1) when G^5, G^6, or G^7 is N, then the respective J^4, J^5, or J^6 is null;

2) when G^2, G^3, or G^4 is O or S, then the respective J^3, J^4 or J^5 is null;

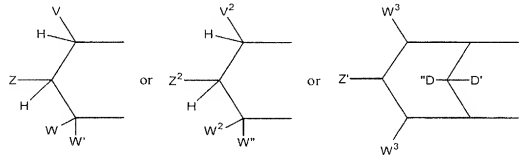
3) when G^3 or G^4 is N, then the respective J^4 or J^5 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

4) if both Y groups are $-NR^6$-, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n$-C(O)-R^{14};

when one Y is $-NR^6$-, and R^1 attached to it is $-(CR^{12}R^{13})_n$-C(O)-R^{14}, then the other YR^1 is selected from the group of $-NR^{15}R^{16}$, $-OR^7$, and NR^{18}-$(CR^{12}R^{13})_n$-C(O)-R^{14};

when only one Y is -O-, which -O- is not part of a cyclic group containing the other Y, the other Y is $-N(R^{18})$-$(CR^{12}R^{13})$-C(O)-R^{14}; and

when either Y is independently selected from -O- and $-NR^6$-, then together R^1 and R^1 are -alkyl-S-S-alkyl- to form a cyclic group, or together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NH$aryl, $-(CH_2)_p$-OR^2, and $-(CH_2)_p$-SR^2, where p is an integer 2 or 3; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

each R^9 is independently selected from the group of -H, alkyl, aralkyl, and alicyclic, or together R^9 and R^9 form a cyclic alkyl group;

R^{11} is selected from the group of alkyl, aryl, $-NR^2_2$, and $-OR^2$; and

each R^{12} and R^{13} is independently selected from the group of H, lower alkyl, lower aryl, lower aralkyl, all optionally substituted, or R^{12} and R^{13} together are connected via a chain of 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S, to form a cyclic group;

each R^{14} is independently selected from the group of $-OR^{17}$, $-N(R^{17})_2$, $-NHR^{17}$, $-SR^{17}$, and $-NR^2OR^{20}$;

R^{15} is selected from the group of –H, lower aralkyl, lower aryl, lower aralkyl, or together with R^{16} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S;

R^{16} is selected from the group of $-(CR^{12}R^{13})_n$-C(O)-R^{14}, -H, lower alkyl, lower aryl, lower aralkyl, or together with R^{15} is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S;

each R^{17} is independently selected from the group of lower alkyl, lower aryl, and lower aralkyl, or together R^{17} and R^{17} on N is connected via 2-6 atoms, optionally including 1 heteroatom selected from the group of O, N, and S;

R^{18} is independently selected from H, lower alkyl, aryl, and aralkyl, or, together, R^{12} and R^{18} are connected via 1-4 carbon atoms to form a cyclic group;

R^{19} is selected from the group of –H, and lower acyl;

R^{20} is selected from the group of –H, lower R^3, and –C(O)-(lower R^3);

R^{21} is selected from the group of –H and lower R^3;

n is an integer from 1 to 3;

with the provisos that:

1) when G^5, G^6, or G^7 is N, then the respective J^4, J^5, or J^6 is null;

2) when X^4 is substituted furanyl, then at least one of J^3, J^4, J^5 and J^6 is not –H or null;

3) when X^4 is not substituted furanyl, then at least two of J^3, J^4, J^5 and J^6 on formula VII-5 or J^3, J^4, J^5, J^6, J^7 on formula VII-6 are not –H or null;

4) when G^2, G^3, or G^4 is O or S, then the respective J^3, J^4, or J^5 is null;

5) when G^3 or G^4 is N, then the respective J^4 or J^5 is not halogen or a group directly bonded to G^3 or G^4 via a heteroatom;

6) if both Y groups are $-NR^6-$, and R^1 and R^1 are not connected to form a cyclic phosphoramidate, then at least one R^1 is $-(CR^{12}R^{13})_n-C(O)-R^{14}$;

7) when X^4 is –alkylcarbonylamino- or -alkylaminocarbonyl-, then G^5, G^6, and G^7 are not all C;

8) when X^4 is –alkoxyalkyl-, and G^5, G^6, and G^7 are all C, then neither J^4 nor J^6 can be substituted with an acylated amine;

9) when R^{55} is substituted phenyl, then J^4, J^5, and J^6 is not purinyl, purinylalkylene, deaza-purinyl, or deazapurinylalkylene;

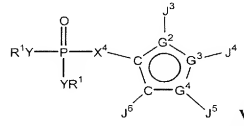
10) R^1 can be lower alkyl only when the other YR^1 is $-NR^{18}-C(R^{12}R^{13})_n-C(O)-R^{14}$;

11) when R^{55} is substituted phenyl and X^4 is 1,2-ethynyl, then J^4 or J^6 is not a heterocyclic group;

12) when X^4 is 1,2-ethynyl, then G^5 or G^7 cannot be N;

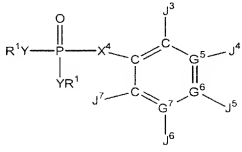
and pharmaceutically acceptable prodrugs and salts thereof.

In one aspect of the present invention compounds of formula VII-1 are envisioned.



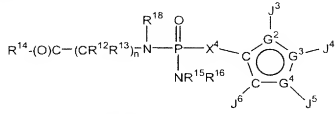
VII-1

In another aspect of the present invention compounds of formula VII-2 are envisioned.



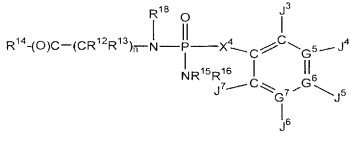
VII-2

In one aspect of the present invention, compounds of the formula VII-1-A are envisioned.



VII-1-A

In another aspect of the present invention compounds of formula VII-2-A are envisioned.



VII-2-A

In one aspect of the present invention compounds of formulae VII-1 or VII-2 are envisioned with the further proviso that when X^4 is -alkoxyalkyl-, and R^{55} is substituted thienyl, substituted furanyl, or substituted phenyl, then J^4, J^5, or J^6 is not halo or alkenyl.

In another aspect are compounds of formula formulae VII-1 or VII-2 with the further proviso that when X^4 is -alkoxyalkyl-, then R^{55} is not substituted thienyl, substituted furanyl, or substituted phenyl.

In yet another aspect are compounds of formulae VII-1 or VII-2 with the further proviso that when X^4 is -alkoxycarbonyl-, and G^5, G^6, and G^7 are all C, then neither J^3 nor J^7 is a group attached through a nitrogen atom.

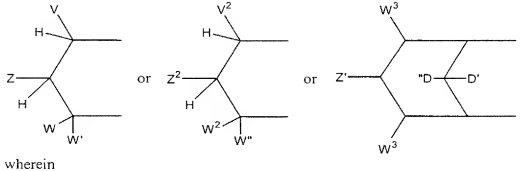
In another aspect are compounds of formulae VII-1 or VII-2 with the further proviso that when X^4 is –alkoxyalkyl- or –alkoxycarbonyl-, then R^{55} is not substituted phenyl.

In one aspect of the invention are compounds of formulae VII-1 or VII-2 wherein when Y is -O-, then R^1 attached to -O- is independently selected from the group of -H, optionally substituted aryl, optionally substituted alicyclic where the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted arylalkylene-,

$-C(R^2)_2OC(O)R^3$, $-C(R^2)_2$-O-C(O)OR^3, $-C(R^2)_2OC(O)SR^3$, -alkyl-S-C(O)R^3, and -alkyl-S-S-alkylhydroxy;

when Y is $-NR^6$-, then R^1 attached to $-NR^6$- is independently selected from the group of -H, and $-(CR^{12}R^{13})_n$-C(O)R^{14};

or when either Y is independently selected from -O- and $-NR^6$-, then together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

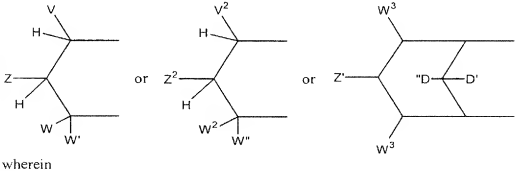
Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, -CH(CH=CR^2_2)OH, -CH(C≡CR^2)OH, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p$-OR^2, and $-(CH_2)_p$-SR^2, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

when Y is -NR^6-, then the R^1 attached to said -NR^6- group is selected from the group of -$C(R^4)_2$-C(O)OR^3, and -$C(R^2)_2C(O)OR^3$; or the other Y group is -O- and then R^1 attached to said -O- is selected from the group of optionally substituted aryl, -$C(R^2)_2OC(O)R^3$, and -$C(R^2)_2OC(O)OR^3$. Within such group are compounds wherein both Y groups are -O-, and R^1 is H.

In another aspect of the invention are compounds wherein at least one Y is -O-, and together R^1 and R^1 are



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of –CHR^2OH , -$CHR^2OC(O)R^3$, -$CHR^2OC(S)R^3$, -$CHR^2OC(S)OR^3$, -$CHR^2OC(O)SR^3$, -$CHR^2OCO_2R^3$, -OR^2 , -SR^2, -CHR^2N_3, -CH_2aryl, -CH(aryl)OH, -CH(CH=CR^2_2)OH, -CH(C≡CR^2)OH, -R^2 , -NR^2_2, -$OCOR^3$, -OCO_2R^3, -$SCOR^3$, -SCO_2R^3, -$NHCOR^2$, -$NHCO_2R^3$, -CH_2NHaryl, -$(CH_2)_p$-OR^2, and -$(CH_2)_p$-SR^2, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OCO_2R^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OC(S)OR^3$, -CH(aryl)OH, $-CH(CH{=}CR^2{}_2)OH$, $-CH(C{\equiv}CR^2)OH$, $-SR^2$, $-CH_2NHaryl$, $-CH_2aryl$; or

together V^2 and Z^2 are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, $-OC(O)R^3$, $-OCO_2R^3$, and $-OC(O)SR^3$;

D' is –H;

D'' is selected from the group of -H, alkyl, $-OR^2$, -OH, and $-OC(O)R^3$;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W'' are not all –H ; and

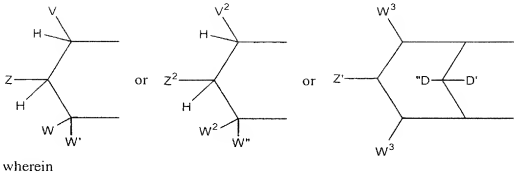
b) both Y groups are not $-NR^6-$;

R^2 is selected from the group of R^3 and -H;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group of -H, and lower alkyl.

In another aspect of the invention are compounds wherein one Y is -O-, and R^1 is optionally substituted aryl; and the other Y is $-NR^6-$, where R^1 attached to said $-NR^6-$ is selected from the group of $-C(R^4)_2C(O)OR^3$, and $-C(R^2)_2C(O)OR^3$. In another aspect are such compounds wherein R^1 attached to -O- is selected from the group of phenyl, and phenyl substituted with 1-2 substituents selected from the group of $-NHC(O)CH_3$, -F, -Cl, -Br, $-C(O)OCH_2CH_3$, and $-CH_3$; and wherein R^1 attached to $-NR^6-$ is $-C(R^2)_2C(O)OR^3$;



wherein

a) V is selected from the group of aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkynyl and 1-alkenyl; or

together V and Z are connected via an additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, said cyclic group is fused to an aryl group at the beta and gamma position to the Y adjacent to V; or

Z is selected from the group of $-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $-CH(CH=CR^2_2)OH$, $-CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2$NHaryl, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$, where p is an integer 2 or 3; or

together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or

W and W' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl and 1-alkynyl; or

together W and W' are connected via an additional 2-5 atoms to form a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

b) V^2, W^2 and W'' are independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

Z^2 is selected from the group of -CHR^2OH, -$CHR^2OC(O)R^3$, -$CHR^2OC(S)R^3$, -$CHR^2OCO_2R^3$, -$CHR^2OC(O)SR^3$, -$CHR^2OC(S)OR^3$, -CH(aryl)OH, -CH($CH=CR^2_2$)OH, -CH($C\equiv CR^2$)OH, -SR^2, -CH_2NHaryl, -CH_2aryl; or

together V^2 and Z^2 are conneeted via an additional 3-5 atoms to form a cyclic group containing 5-7 ring atoms, optionally containing 1 heteroatom, and substituted with hydroxy, acyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from a Y attached to phosphorus;

c) Z' is selected from the group of -OH, -$OC(O)R^3$, -OCO_2R^3, and -$OC(O)SR^3$;

D' is –H;

D" is selected from the group of -H, alkyl, -OR^2, -OH, and -$OC(O)R^3$;

each W^3 is independently selected from the group of -H, alkyl, aralkyl, alicyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, and 1-alkynyl;

with the provisos that:

a) V, Z, W, W' are not all –H and V^2, Z^2, W^2, W" are not all –H ; and

b) both Y groups are not -NR^6-;

R^2 is selected from the group of R^3 and -H;

R^3 is selected from the group of alkyl, aryl, alicyclic, and aralkyl;

R^6 is selected from the group of -H, and lower alkyl.

In another aspect, R^{55} is substituted phenyl; X^4 is furan-2,5-diyl; J^3, J^4, J^5, J^6, and J^7 are independently selected from the group of –OR^3, -SO_2NHR^7, -CN, -H, halo, -NR^4_2, -(CH_2)aryl, -$(CH_2)NH$aryl, and –NO_2; at least one Y group is –O-; and pharmaceutically acceptable salts and prodrugs thereof.

In another aspect of the invention are such compounds wherein when Y is -O-, then R^1 attached to -O- is independently selected from the group of -H, optionally substituted phenyl, -$CH_2OC(O)$-tBu, -$CH_2OC(O)$Et, and -$CH_2OC(O)$OiPr;

when Y is -NR^6-, then R^1 is attached to -NR^6- independently selected from the group of -$C(R^2)_2C(O)OR^3$, -$C(R^4)_2C(O)OR^3$, or

when Y is -O- or -NR^6-, and at least one Y is -O-, then together R^1 and R^1 are

Table M. Table of Sub-Markush Groups for the Y Variable

Sub-Markush Group	Y
1	both Y groups are -O-
2	both Y groups are $-NR^6-$
3	Y is –O- located adjacent to the W', W, W'', and W^2 groups
4	Y is -O- located adjacent to the V group or V^2 group
5	one Y is $-NR^6-$, and one Y is –O-
6	one Y is $-NR^6-$, and the other YR^1 is $-NR^{15}R^{16}$, $-OR^7$ or $NR^{18}-(CR^{12}R^{13})_n-C(O)-R^{14}$
7	one Y is $-NR^6-$, and the other YR^1 is $-NR^{15}R^{16}$, and R^{15} is not H
8	one Y is $-NR^6-$, and the other YR^1 is $-NR^{15}R^{16}$, and R^{16} is $-(CR^{12}R^{13})_n-C(O)-R^{14}$
9	both Y groups are the same $-NR^6-$, such that the phosphonate prodrug moiety has a plane of symmetry through the phosphorus-oxygen double bond
10	one Y is $-NR^6-$, and the other YR^1 is $-NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is a cyclic amine
11	one Y is $-NR^6-$, and the other YR^1 is $-NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is selected from the group of morpholinyl and pyrrolidinyl
12	one Y is $-NR^6-$, and the other YR^1 is $-NR^{15}R^{16}$, where $-NR^{15}R^{16}$ is $-(CR^{12}R^{13})_n-C(O)R^{14}$

Table N. Table of Sub-Markush Groups for the Z Variable

Sub-Markush Group	Z
1	$-OR^2$, $-SR^2$, $-R^2$, $-NR^2_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$
2	$-OR^2$, $-R^2$, $-OC(O)R^3$, $-OCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$
3	$-OR^2$, -H, $-OC(O)R^3$, $-OCO_2R^3$, and $-NHC(O)R^2$
4	$-CHR^2OH$, $-CHR^2O-C(O)R^3$, and $-CHR^2O-CO_2R^3$
5	$-CHR^2OH$, $-CHR^2OC(O)R^3$, $-CHR^2OC(S)R^3$, $-CHR^2OC(S)OR^3$, $-CHR^2OC(O)SR^3$, $-CHR^2OCO_2R^3$, $-OR^2$, $-SR^2$, $-CHR^2$, $-CHR^2N_3$, $-CH_2$aryl, -CH(aryl)OH, $CH(CH=CR^2_2)OH$ $CH(C\equiv CR^2)OH$, $-R^2$, $-NR^2_2$, $-OCOR^3$, $-OCO_2R^3$, $-SCOR^3$, $-SCO_2R^3$, $-NHCOR^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)p-OR^2$ and $-(CH_2)p-SR^2$
6	$-OR^2$, $-SR^2$, $-CHR^2N_3$, $-R^2$, $-OC(O)R^2$, $-OCO_2R^3$, $-SC(O)R^3$,$-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NHaryl$,$-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$
7	$-OR^2$, $-R^2$, $-OC(O)R^3$,$-OCO_2R^3$, $-CH_3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-(CH_2)_p-OR^2$, and $-(CH_2)_p-SR^2$
8	-H, OR^2, and $-NHC(O)R^2$
9	-H
10	together V and Z are connected via an additional 3-5 atoms, optionally including 1 heteroatom, to form a cyclic group that is fused to an aryl group at the beta and gamma position to the Y group
11	together Z and W are connected via an additional 3-5 atoms to form a cyclic group, optionally containing one heteroatom, and V is aryl, substituted aryl, heteroaryl or substituted heteroaryl

Table O. Table of Sub-Markush Groups for the Z' Variable

Sub-Markush Group	Z'
1	$-OR^2$, $-SR^2$, $-R^2$, $-NR^2{}_2$, $-OC(O)R^3$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$
2	$-OR^2$, $-R^2$, $-OC(O)R^3$, $-OCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$
3	$-OR^2$, -H, $-OC(O)R^3$, $-OCO_2R^3$, and $-NHC(O)R^2$
4	$-CHR^2OH$, $-CHR^2O-C(O)R^3$, and $-CHR^2O-CO_2R^3$
5	-OH, $-OC(O)R^3$, $-OCO_2R^3$ and $-OC(O)SR^3$
6	-OH, $-OC(O)R^3$, and $-OCO_2R^3$
7	$-OR^2$, $-SR^2$, $-CHR^2N_3$, $-R^2$, $-OC(O)R^2$, $-OCO_2R^3$, $-SC(O)R^3$, $-SCO_2R^3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-CH_2NHaryl$, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$
8	$-OR^2$, $-R^2$, $-OC(O)R^2$, $-OCO_2R^3$, $-CH_3$, $-NHC(O)R^2$, $-NHCO_2R^3$, $-(CH_2)_p-OR^{19}$, and $-(CH_2)_p-SR^{19}$
9	-H, OR^2, and $-NHC(O)R^2$
10	-H

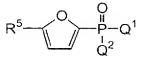
Diphenyl esters;
Bis-(2-methylphenyl) esters;
Bis-(2-methoxyphenyl) esters;
Bis-(2-ethoxyphenyl) esters;
Bis-(4-methoxyphenyl) esters;
Bis-(3-bromo-4-methoxybenzyl) esters;
Bis-(4-acetoxybenzyl) esters;
Bis-(3,5-dimethoxy-4-acetoxybenzyl) esters;
Bis-(3-methyl-4-acetoxybenzyl) esters;
Bis-(3-methoxy-4-acetoxybenzyl) esters;
Bis-(3-chloro-4-acetoxybenzyl) esters;
Bis-(cyclohexyloxycarbonyloxymethyl) esters;
Bis-(isopropyloxycarbonyloxymethyl) esters;
Bis-(ethyloxycarbonyloxymethyl) esters;
Bis-(methyloxycarbonyloxymethyl) esters;
Bis-(isopropylthiocarbonyloxymethyl) esters;
Bis-(phenyloxycarbonyloxymethyl) esters;
Bis-(benzyloxycarbonyloxymethyl) esters;
Bis-(phenylthiocarbonyloxymethyl) esters;
Bis-(*p*-methoxyphenoxycarbonyloxymethyl) esters;
Bis-(*m*-methoxyphenoxycarbonyloxymethyl) esters;
Bis-(*o*-methoxyphenoxycarbonyloxymethyl) esters;
Bis-(*o*-methylphenoxycarbonyloxymethyl) esters;
Bis-(*p*-chlorophenoxycarbonyloxymethyl) esters;
Bis-(1,4-biphenoxycarbonyloxymethyl) esters;
Bis-[(2-phthalimidoethyl)oxycarbonyloxymethyl]esters;
Bis-(6-hydroxy-3,4-dithia)hexyl esters;
Cyclic-(3,4-dithiahexan-1,6-diyl) esters;
Bis-(2-bromoethyl) esters;
Bis-(2-aminoethyl) esters;
Bis-(2-*N*,*N*-diaminoethyl) esters;
O-phenyl-[N-(1-ethoxycarbonyl)ethyl]phosphoramidates (-P(O)(OPh)-(NH-*CH(Me)CO_2Et)
O-phenyl-[N-(1-methoxycarbonyl)ethyl]phosphoramidates (-P(O)(OPh)-(NH-*CH(Me)CO_2Me)
O-(3-chlorophenyl)-[N-(1-ethoxycarbonyl)ethyl]phosphoramidates (-P(O)(OPh-3-Cl)-(NH-*CH(Me)CO_2Et)
O-(2-chlorophenyl)-[N-(1-ethoxycarbonyl)ethyl]phosphoramidates (-P(O)(OPh-2-Cl)-(NH-*CH(Me)CO_2Et)
O-(4-chlorophenyl)-[N-(1-ethoxycarbonyl)ethyl]phosphoramidates (-P(O)(OPh-4-Cl)-(NH-*CH(Me)CO_2Et)
O-(4-acetamidophenyl)-[N-(1-ethoxycarbonyl)ethyl]phosphoramidates (-P(O)(OPh-4-NHAc)(NH-*CH(Me)CO_2Et)
O-(2-ethoxycarbonylphenyl)-[N-(1-ethoxycarbonyl)ethyl]phosphoramidates (-P(O)(OPh-2-CO_2Et)(NH-*CH(Me)CO_2Et)

O-phenyl-[N-(1-ethoxycarbonyl-1-methyl)ethyl]phosphoramidates (-P(O)(OPh)(NH-C(Me)$_2$CO$_2$Et)
O-phenyl-[N-(1-methoxycarbonyl-1-methyl)ethyl]phosphoramidates (-P(O)(OPh)(NH-C(Me)$_2$CO$_2$Me)
O-(3-chlorophenyl)-[N-(1-ethoxycarbonyl-1-methyl)ethyl]phosphoramidates (-P(O)(OPh-3-Cl)(NH-C(Me)$_2$CO$_2$Et)
O-(2-chlorophenyl)-[N-(1-ethoxycarbonyl-1-methyl)ethyl]phosphoramidates (-P(O)(OPh-2-Cl)(NH-C(Me)$_2$CO$_2$Et)
O-(4-chlorophenyl)-[N-(1-ethoxycarbonyl-1-methyl)ethyl]phosphoramidates (-P(O)(OPh-4-Cl)(NH-C(Me)$_2$CO$_2$Et)
O-(4-acetamidophenyl)-[N-(1-ethoxycarbonyl-1-methyl)ethyl]phosphoramidates (-P(O)(OPh-4-NHAc)(NH-C(Me)$_2$CO$_2$Et)
O-(2-ethoxycarbonylphenyl)-[N-(1-ethoxycarbonyl-1-methyl)ethyl]-phosphoramidates (-P(O)(OPh-2-CO$_2$Et)(NH-C(Me)$_2$CO$_2$Et)

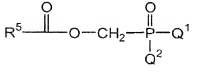
In the above prodrugs an asterisk (*) on a carbon refers to the L-configuration.

O-phenyl-[N-(ethoxycarbonyl)methyl]phosphoramidates (-P(O)(OPh)(NH-CH$_2$CO$_2$Et)
O-phenyl-[N-(methoxycarbonyl)methyl]phosphoramidates (-P(O)(OPh)(NH-CH$_2$CO$_2$Me)
O-(3-chlorophenyl)-[N-(ethoxycarbonyl)methyl]phosphoramidates (-P(O)(OPh-3-Cl)-(NH-CH$_2$CO$_2$Et)
O-(2-chlorophenyl)-[N-(ethoxycarbonyl)methyl]phosphoramidates (-P(O)(OPh-2-Cl)-(NH-CH$_2$CO$_2$Et)
O-(4-chlorophenyl)-[N-(ethoxycarbonyl)methyl]phosphoramidates (-P(O)(OPh-4-Cl)-(NH-CH$_2$CO$_2$Et)
O-(4-acetamidophenyl)-[N-(ethoxycarbonyl)methyl]phosphoramidates (-P(O)(OPh-4-NHAc)(NH-CH$_2$CO$_2$Et)
O-(2-ethoxycarbonylphenyl)-[N-(ethoxycarbonyl)methyl]phosphoramidates (-P(O)(OPh-2-CO$_2$Et)(NH-CH$_2$CO$_2$Et)

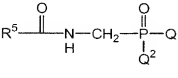
The compounds designated in Table 1 refer to preferred compounds of formula I-A where M is R^5-X- as defined in the following formulae: formula i, formula ii, and formula iii, wherein Q^1 and Q^2 correspond to $NR^{15}N^{16}$ and $N(R^{18})$-$(CR^{12}R^{13})_n$-C(O)-R^{14} of formula I-A.



Formula i



Formula ii



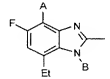
Formula iii

In the above formulae i, ii, and iii, R^5 may be substituted by A and B. The preferred compounds of formulae i, ii, and iii are listed in Table 1 by designated numbers assigned to R^5, A, B, Q^1, and Q^2 in the above formulae i, ii, and iii according to the following convention: $Q^1.Q^2.$ $R^5.B.A.$ For each moiety, structures are assigned to a number shown in the following tables for R^5, A, B, Q^1 and Q^2.

Variable R^5 is divided into two groups, each listing four different structures.

Compounds named in Table 1 of formulae i, ii, and iii wherein the R^5 moieties are assigned the following numbers:

Group 1:

	1	2	3	4
R^5				

Group 2:

	1	2	3	4
R^5=				

Variable A moieties are assigned the following numbers:

	1	2	3	4
A=	NH_2	H	Me	Cl

Variable B moieties are assigned the following numbers:

	1	2	3	4	5	6	7	8
B=	-SCH_3	-*t*Bu	-*c*Pr	-S-*n*Pr	-SEt	-iPr	-nPr	-CH_2cPr

Variables Q^1 and Q^2 are divided into three groups, each listing eight different substituents.

Q^1 and Q^2 moieties are assigned the following numbers:

Group 1:

Q^1 and Q^2

1. -NH-CH_2-C(O)R^{14}
2. -NH-$CH(CH_3)$-C(O)R^{14}
3. -NH-$C(CH_3)_2$-C(O)R^{14}
4. -NH-$C(CH_3)_2CH_2$-C(O)R^{14}
5. -NH-$CH(CH(CH_3)_2)$-C(O)R^{14}
6. -NH-$CH(CH_2(CH(CH_3)_2))$-C(O)R^{14}
7. -NH-$CH(CH_2CH_2SCH_3)$-C(O)R^{14}
8. -NH-$CH(CH_2SCH_2Ph)$-C(O)R^{14}

Group 2:

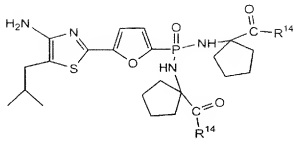
Q^1 and Q^2

1. -NH-CH_2CH_2-C(O)R^{14}
2. -NH-$CH(CH_2CH_2COR^{14})$-C(O)R^{14}
3. -NH-$CH(CH_2COR^{14})$-C(O)R^{14}
4. -NH-$CH(CH_2CONH_2)$-C(O)R^{14}
5. -NH-$CH(COR^{14})CH_2$-C(O)R^{14}
6. -NH-$CH(CH_2OR^{17})$-C(O)R^{14}
7. -NH-$CH(CH_2CH_2COR^{14})$-C(O)R^{14}
8. -NH-$CH(CH_2OH)$-C(O)R^{14}

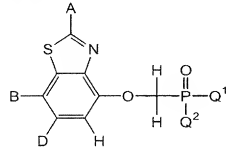
Group 3:

Q^1 and Q^2

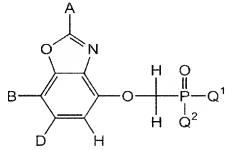
1. -NH-$CH(CH_2$-$C_6H_5OH)$-C(O)R^{14}
2. -NH-C(c-propyl)-C(O)R^{14}
3. -NH-C(c-pentyl)-C(O)R^{14}
4. -NH-C(c-hexyl)-C(O)R^{14}
5. -NH-$CH(CH_2Ph)$-C(O)R^{14}
6. -N(CH_3)-CH_2-C(O)R^{14}



The numbers designated in Table 1 also refer to preferred benzothiazole and benzoxazole compounds of formula X. These preferred compounds are shown in formulae iv and v.



Formula iv



Formula v

The preferred compounds of formulae iv and formula v are listed in Table 1 by designated numbers assigned to A, B, D, Q^1, and Q^2 in the above formulae iv and v according to the following convention: $Q^1.Q^2.A.B.D$. For each moiety, structures assigned to a number shown in the following tables for A, B, D, Q^1 and Q^2.

Variables Q^1 and Q^2 are divided into three groups, each listing eight different substituents. Q^1 and Q^2 moieties are assigned the following numbers:

Group 1:

Q^1 and Q^2

1. $-NH-CH_2-C(O)R^{14}$
2. $-NH-CH(CH_3)-C(O)R^{14}$
3. $-NH-C(CH_3)_2-C(O)R^{14}$
4. $-NH-C(CH_3)_2CH_2-C(O)R^{14}$
5. $-NH-CH(CH(CH_3)_2))-C(O)R^{14}$

and allows the insulin secretagogue to become more fully effective over time and in the long term thus provides improved response to the insulin secretagogue and enhanced glycemic control.

Another important benefit of insulin secretagogue-FBPase inhibitor combination treatment is an unexpected beneficial effect on carbohydrate, and/or lipid, and/or protein metabolism.

Another benefit of the combination therapy is that FBPase inhibitors can attenuate the side effects associated with insulin secretagogue therapy, and vice versa. A key consequence of insulin secretagogue therapy is hyperinsulinemia which results in the undesirable side effects of promoting weight gain, of exacerbating insulin resistance, and of predisposing patients to hypoglycemic episodes. Hyperinsulinemia may also be associated with increased risk of macrovascular disease. Insulin secretagogues can also overstimulate the pancreas and consequently promote beta cell degeneration and thus secondary failure. Likewise, FBPase inhibitors may have undesirable side effects in man. FBPase inhibitors may, for instance, cause a transient rise in blood lactate levels. As described in Example X, combination therapy of an FBPase inhibitor and an insulin secretagogue (glyburide) resulted in an unexpeeted attenuation of the blood lactate elevation caused by FBPase inhibitor monotherapy .

Insulin/Insulin Analogues

In another aspect, preferred is the use of an FBPase inhibitor and insulin or an insulin analogue. Insulin is a polypeptide hormone (Molecular weight ~ 6000) that is released into the circulation by the pancreatic beta cell in response to key metabolic fuels such as amino acids, three-carbon sugars such as glyceraldehyde, and most importantly by glucose. The key physiological role of insulin is the regulation of glucose homeostasis. Insulin, once seereted, binds to specific receptors present on cell surfaces and through a complex signaling cascade regulates a variety of processes including the uptake of glucose by tissues such as muscle and fat, and the inhibition of glucose production by the liver ("hepatic glucose production" or HGO). Insulin is believed to inhibit HGO primarily by reducing flux through the pathway of *de novo* glucose production, or gluconeogenesis. Its effects on gluconeogenesis are mediated by multiple mechanisms including: (a) a

compounds of the biguanide class that have this readily demonstrable activity are used in this invention. Preferred biguanides inhibit gluconeogenesis from lactate in rat hepatocytes in the presence of insulin with an IC_{50} of 10 nM to 100 microM in the assay described by Wollen N, Bailey CJ, Biochem. Pharmacol. 37: 4353-4358 (1998). More preferred have an IC_{50} between 1 microM and 30 microM. Preferred biguanides also counteract glucacon-stimulated glucose production from lactate in rat hepatocytes. Yu B, Pugazhenthi S, Khandlewal RL, Biochem. Pharmacol. 48: 949-954 (1994). Preferred compounds have an IC_{50} of 0.1 to 5000 microM. Most preferred have an IC_{50} of 0.1 to 500 microM.

In another aspect, preferred is the use of an FBPase inhibitor and a biguanide. Metformin is a biguanide that has been in use for the treatment of NIDDM since 1957. For many years it was believed that the glucose lowering effects of metformin resulted from improved peripheral insulin sensitivity and decreased post-prandial carbohydrate absorption. It is now believed that metformin acts primarily by decreasing endogenous glucose production. Inzucchi SE, Maggs DG, Spollett GR et al, N. Engl. J. Med. 338: 867-872 (1998). There is a substantial body of evidence that the effects of metformin on endogenous glucose production are the result of the inhibition of hepatic gluconeogenesis. Studies in isolated perfused livers and hepatocytes from animals have shown that metformin, via a mechanism that is synergistic with insulin, reduces gluconeogenesis from a range of substrates including lactate, pyruvate, alanine, glutamine, and glycerol. Wiernsperger NF and Bailey CJ Drugs 58 (suppl. 1): 31-39 (1999). A recent study of type 2 diabetics has also indicated that metformin inhibits endogenous glucose production via a reduction in gluconeogenesis. Hundal RS, Krassak M, Laurent D et al. Diabetes 49 (suppl. 1) 154 OR (2000). The mechanism by which this inhibitory effect is exerted is unclear and has been postulated to involve decreased hepatic uptake of gluconeogenic precursors and/or the stimulation of pyruvate kinase and hence the opposing pathway of glycolysis.

Metformin was one of the therapies evaluated in the U.K. Prospective Diabetes Study (UKPDS) which examined whether intensive glycemic control of type 2 diabetic patients reduces the incidence of clinical complications. The findings of this large multi-center trial were reported in 1998 and showed that while metformin initially provided

While such disclosures constitute a large number of glucagon antagonists, the instant invention is not so limited and can utilize any glucagon antagonists. Examples of known glucagon antagonists include ALT-3000 (Alteon, Inc.), BAY-27-9955 (Bayer, AG), CP-99711, Skyrin, and NNC-92-1687. The methods used to identify and characterize glucagon antagonists are also well known (e.g., see Example S) and have been extensively described.

Glucagon antagonists inhibit glucagon binding to baby hamster kidney cells transfected with the human glucagon receptor (Example S). Preferred antagonists have IC_{50}'s between 0.1 nM and 100 microM. More preferred compounds inhibit binding with IC_{50}'s between 0.1 nM and 1 microM.

Although glucagon antagonists act primarily by inhibiting hepatic glucose production, combination treatment of an FBPase inhibitor and a glucagon antagonist surprisingly results in significantly greater glycemic control than administration of either agent alone.

Another important benefit of FBPase inhibitor-glucagon antagonist combination treatment is an unexpected beneficial effect on carbohydrate, and/or lipid, and/or protein metabolism.

Another benefit of the combination therapy is that FBPase inhibitors can attenuate the side effects associated with glucagon antagonist therapy, and vice versa.

As described above, glucagon is an important regulator of hepatic glucose production. Basal glucagon levels are higher in type NIDDM than in control subjects, despite the concurrent basal hyperglycemia and hyperinsulinemia, two factors known to suppress glucagon secretion. Reaven GM, Chen YD, Golay A, Swislocki AL, Jaspan JB, J Clin Endocrinol Metab 64: 106-110 (1987). A direct relationship between plasma glucagon concentrations and blood glucose levels has been found in NIDDM. In addition, it has been shown that glucagon may be responsible for sustaining up to 60% of the elevated rates of hepatic glucose production evident in type NIDDM patients. Baron AD, Schaeffer L, Shragg P, Kolterman OG, Diabetes 36: 274-283 (1987). Glucagon secretion from pancreatic alpha cells is inhibited by insulin from beta cells.

Amylin/Amylin Agonists

Deems RO, Anderson RC, Foley JE Am. J. Physiol. 274: R524-528 (1998)

This invention is not limited to the CPT I inhibitors described above but can use any inhibitor of CPT I or other compounds that inhibit fatty acid oxidation. The methods used to identify and characterize fatty acid oxidation inhibitors are well known and have been extensively described.

Preferred fatty acid oxidation inhibitors have an IC_{50} of 10 nM to 300 microM in the palmitate oxidation assay in rat hepatocytes (Example U). More preferred have an IC_{50} between 10 nM and 30 microM.

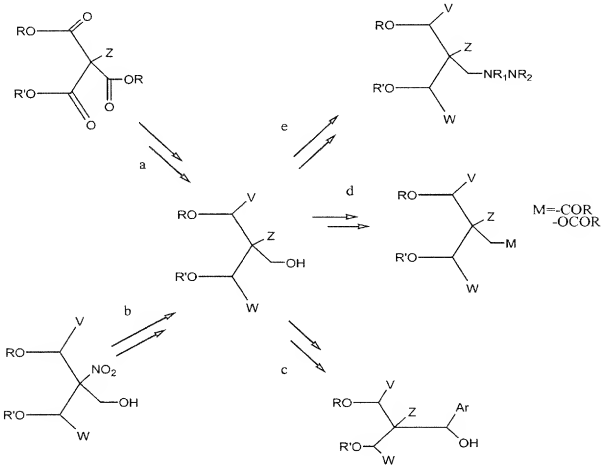
Although fatty acid oxidation inhibitors are known to inhibit hepatic glucose production, combination treatment of an FBPase inhibitor and fatty acid oxidation inhibitor surprisingly results in significantly greater glycemic control than administration of either agent alone (Example JJ).

Another important benefit of FBPase inhibitor-fatty acid oxidation inhibitor combination treatment is an unexpected beneficial effect on carbohydrate, and/or lipid, and/or protein metabolism.

Another benefit of the combination therapy is that FBPase inhibitors can attenuate the side effects associated with fatty acid oxidation inhibitor therapy, and vice versa. Fatty acid oxidation inhibitor treatment has been known, for instance, to be associated with cardiac hypertrophy. Bressler R, Gay R, Copeland G et al Life Sci 44: 1897-1906 (1989).

FBPase inhibitors lower blood glucose both in the fasted state (Examples E-G) the freely-feeding state (Example W), and postprandial state (Example X). This provides a broad opportunity for therapy in combination with insulin secretagogues, insulin, biguanides, alpha-glucosidase inhibitors, glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, amylin agonists, or fatty acid oxidation inhibitors. The combination could, be administered at mealtime, for instance, and provide enhanced glycemic control over either agent alone. Another possible dosing regimen may be the administration of the insulin secretagogue, insulin, biguanide, glycogen phosphorylase inhibitor, glucose-6-phosphatase inhibitor, glucagon antagonist, amylin agonist, or fatty acid oxidation inhibitor during the daytime, and administration of the FBPase inhibitor separately at night. Many other dosing regimens are possible.

methyl chloroformate) (path d) using known chemistry (Greene et al., *Protective Groups In Organic Synthesis* ; Wiley, New York, **1990**). Other functional group manipulations can also be used to prepare 1,3-propanediols such as oxidation of one the hydroxylmethyl groups in a 2-(hydroxymethyl)-1,3-propanediol to an aldehyde followed by addition reactions with an aryl Grignard (path c). Aldehydes can also be converted to alkyl amines via reductive amination reactions (path e).



Known amide bond formation reactions (e.g., the acyl halide method, the mixed anhydride method, the carbodiimide method) can also be used to couple a heteroaromatic carboxylic acid with a phosphonate diester component leading to compounds of formula 4 wherein X is an alkylaminocarbonyl or an alkoxycarbonyl group. For example, couplings of a thiazole-4-carboxylic acid with a dialkyl aminoalkylphosphonate or a dialkyl hydroxyalkylphosphonate give compounds of formula 4 wherein R^5 is a thiazole, and X is an alkylaminocarbonyl or an alkoxycarbonyl group. Alternatively, the nature of the coupling partners can be reversed to give compounds of formula 4 wherein X is an alkylcarbonylamino group. For example, 2-aminothiazoles can be coupled with $(RO)_2P(O)$-alkyl-CO_2H (e.g., diethylphosphonoacctic acid) under these reaction conditions to give compounds of formula 4 wherein R^5 is a thiazole and X is an alkylcarbonylamino group. These reactions are also useful for parallel synthesis of compound libraries through combinatorial chemistry on solid phase or in solution phase. For example, $HOCH_2P(O)(OEt)$(O-resin) , $H_2NCH_2P(O)(OEt)$(O-resin) and $HOOCCH_2P(O)(OEt)$(O-resin) (prepared using known methods) can be coupled to various heterocycles using the above described reactions to give libraries of compounds of formula 3 wherein X is a $-C(O)OCH_2-$, or a $-C(O)NHCH_2-$, or a $-NHC(O)CH_2-$.

Rearrangement reactions can also be used to prepare compounds covered in the present invention. For example, the Curtius's rearrangement of a thiazole-4-carboxylic acid in the presence of a dialkyl hydroxyalkylphosphonate or a dialkyl aminoalkylphosphonate lead to compounds of formula 4 wherein X is an alkylaminocarbonylamino or an alkoxycarbonylamino group. These reactions can also be adoptcd for combinatorial synthesis of various libraries of compounds of formula 3. For example, Curtius's rearrangement reactions between a heterocyclic carboxylic acid and $HOCH_2P(O)(OEt)$(O-resin), or $H_2NCH_2P(O)(OEt)$(O-resin) can lead to libraries of compounds of formula 1 wherein X is a $-NHC(O)OCH_2-$, or a $-NHC(O)NHCH_2-$.

For compounds of formula V wherein X is an alkyl group, the phosphonate group can be introduced using other common phosphonate formation methods such as Michaelis-Arbuzov reaction (Bhattacharya et al., *Chem. Rev.*, **1981**, *81*: 415), Michaelis-Becker reaction (Blackburn et al., *J. Organomet. Chem.*, **1988**, *348*: 55), and addition reactions of

reactions are generally used to synthesize imidazoles such as reactions between amidines and alpha-haloketones (Mallick et al, *J. Am. Chem. Soc.*, **1984**, *106(23)*, 7252) or alpha-hydroxyketones (Shi et al, *Synthetic Comm.*, **1993**, *23(18)*, 2623), reactions between urea and alpha-haloketones, and reactions between aldehydes and 1,2-dicarbonyl compounds in the presence of amines.

(vi) Construction of an isoxazole ring system

Isoxazoles useful for the synthesis of compounds of formula V-1 are readily synthesized using various methodologies (such as cycloaddition reactions between nitrile oxides and alkynes or active methylene compounds, oximation of 1,3-dicarbonyl compounds or alpha, beta-acetylenic carbonyl compounds or alpha,beta-dihalocarbonyl compounds, etc.) can be used to synthesize an isoxazole ring system (Grunanger et al., *Isoxazoles*; Wiley & Sons, New York, **1991**). For example, reactions between alkynes and 5-diethylphosphono-2-chlorooximidofuran in the presence of base (e.g., triethylamine, Hunig's base, pyridine) are useful for the synthesis of compounds of formula 2 wherein R^5 is an isoxazole and X is a furan-2,5-diyl group.

(vii) Construction of a pyrazole ring system

Pyrazoles useful for the synthesis of compounds of formula V-1 are readily prepared using a variety of methods (Wiley, *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings*; Interscience Publishers, New York, **1967**) such as reactions between hydrazines and 1,3-dicarbonyl compounds or 1,3-dicarbonyl equivalents (e.g., one of the carbonyl group is masked as an enamine or ketal or acetal), and additions of hydrazines to acrylonitriles followed by cyclization reactions (Dorn et al, *Org. Synth.*, **1973**, *Coll. Vol. V*, 39). Reaction of 2-(2-alkyl-3-N,N-dimethylamino)acryloyl-5-diethylphosphonofurans with hydrazines are useful for the synthesis of compounds of formula I wherein R^5 is a pyrazole, X is a furan-2,5-diyl group and B" is an alkyl group.

(viii) Construction of a 1,2,4-triazole ring system

1,2,4-Triazoles useful for the synthesis of compounds of formula V-1 are readily available via various methodologies (Montgomery, 1,2,4-Triazoles; Wiley, New York, **1981**). For example, reactions between hydrazides and imidates or thioimidates (Sui et al, *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1929; Catarzi et al, *J. Med. Chem.*, **1995**, *38(2)*, 2196),

(e.g., 5-diethylphosphono-2-furoic acid) by conversion of the acid to the corresponding acyl chloride and followed by additions of a Grignard reagent.

Some of the above described intermediates can also be used for the synthesis of other useful intermediates. For example, a 2-keto-5-dialkylphosphonofuran can be further converted to a 1,3-dicarbonyl derivative which is useful for the preparation of pyrazoles, pyridines or pyrimidines. Reaction of a 2-keto-5-dialkylphosphonofuran (e.g., 2-acetyl-5-diethylphosphonofuran) with a dialkylformamide dialkyl acetal (e.g., dimethylformamide dimethyl acetal) gives a 1,3-dicarbonyl equivalent as a 2-(3-dialkylamino-2-alkyl-acryloyl)-5-dialkylphosphonofuran (e.g., 2-(3-dimethylaminoacryloyl)-5-diethylphosphonofuran).

It is envisioned that the above described methods for the synthesis of furan derivatives can be either directly or with some modifications applied to syntheses of various other useful intermediates such as aryl phosphonate esters (e.g., thienyl phosphonate esters, phenyl phosphonate esters or pyridyl phosphonate esters).

It is conceivable that when applicable the above described synthetic methods can be adopted for parallel synthesis either on solid phase or in solution to provide rapid SAR (structure activity relationship) exploration of FBPase inhibitors encompassed in the current invention, provided method development for these reactions are successful.

Several methods can be used to convert various anilines to benzothiazoles (Sprague, J. M.; Land, A. H. *Heterocycle. Compd. 5*, 506-13, **1957**). For example, 2-aminobezothiazoles (formula 3 wherein A = NH_2) can be prepared by annulation of compounds of formula 4 wherein W^2 = H, using various common methods. One method involves the treatment of a suitably substituted aniline with a mixture of KSCN and $CuSO_4$ in methanol to give a substituted 2-aminobenzothiazole (Ismail, I. A.; Sharp, D. E; Chedekel, M. R. *J. Org. Chem. 45*, 2243-2246, **1980**). Alternatively, a 2-aminobenzothiazole can also be prepared by the treatment of Br_2 in presence of KSCN in acetic acid (Patil, D. G.; Chedekel, M. R. *J. Org. Chem. 49*, 997-1000, **1984**). This reaction can also be done in two step sequence. For example treatment of substituted phenylthioureas with Br_2 in $CHCl_3$ gives substituted 2-aminobenzothiazoles (Patil, D. G.; Chedekel, M. R. *J. Org. Chem. 49*, 997-1000, 1984). 2-Aminobenzothiazoles can also be made by condensation of *ortho* iodo anilines with thiourea in presence of Ni catalyst ($NiCl_2$ $(PPh_3)_2$) (Takagi, K. *Chem. Lett.* 265-266, **1986**).

Benzothiazoles can undergo electrophilic aromatic substitution to give 6-substituted benzothiazoles (Sprague, J. M.; Land, A. H. *Heterocycle. Compd. 5*, 606-13, **1957**). For example bromination of formula 3 wherein G"=S, A=NH_2, L^2,E^2,J^2=H, X^2=CH_2O and R'=Et with bromine in polar solvents such as AcOH gave compound of formula 3 wherein E^2=Br.

Furthermore, compounds of formula 3 wherein A is a halo, H, alkoxy, alkylthio or an alkyl can be prepared from the corresponding amino compound (Larock, *Comprehensive organic transformations*, VCH, New York, **1989**; Trost, *Comprehensive organic synthesis*; Pergamon press, New York, **1991**).

(ii) Benzoxazoles

Compounds of formula 3 wherein G"=O, i.e. benzoxazoles, can be prepared by the annulation of *ortho* aminophenols with suitable reagent (e.g., cyanogen halide (A=NH_2; Alt, K. O.; et al *J. Heterocyclic Chem. 12*, 775, **1975**) or acetic acid (A=CH_3; Saa, J. M.; *J. Org. Chem. 57*, 589-594, **1992**) or trialkyl orthoformate (A=H; *Org. Prep. Proced. Int., 22*, 613, **1990**)).

formate (1.5 mmole) was added and the reaction was stirred for 1 h. Extraction and chromatography gave compound **1** as a clear yellow oil. Preferably this aldehyde can be prepared from 2-furaldehyde as described below.

Step E. A solution of 2-furaldehyde (1 mmole) and N,N'-dimethylethylene diamine (1 mmole) in toluene was refluxed while the resulting water being collected through a Dean-Stark trap. After 2 h the solvent was removed in vacuo and the residue was distilled to give furan-2-(N,N'-dimethylimidazolidine) as a clear colorless oil. bp 59 - 61 °C (3 mm Hg).

Step F. A solution of furan-2-(N,N'-dimethylimidazolidine) (1 mmole) and TMEDA (1 mmole) in THF was treated with nBuLi (1.3 mmole) at -40 to -48 °C. The reaction was stirred at 0 °C for 1.5 h and then cooled to -55 °C and treated with a solution of diethylchlorophosphate (1.1 mmole) in THF. After stirring at 25 °C for 12 h the reaction mixture was evaporated and subjected to extraction to give 5-diethylphosphono-furan-2-(N,N'-dimethylimidazolidine) as a brown oil.

Step G. A solution of 5-diethylphosphonofuran-2-(N,N'-dimethyl- imidazolidine) (1 mmole) in water was treated with concentrated sulfuric acid until pH = 1. Extraction and chromatography gave compound **1** as a clear yellow oil.

Example 2

Preparation of 5-diethylphosphono-2-[(1-oxo)alkyl]furans and 6-diethylphosphono-2-[(1-oxo)alkyl]pyridines.

Step A. A solution of furan (1.3 mmole) in toluene was treated with 4-methyl pentanoic acid (1 mmole), trifluoroacetic anhydride (1.2 mmole) and boron trifluoride etherate (0.1 mmole) at 56 °C for 3.5 h. The cooled reaction mixture was quenched with aqueous sodium bicarbonate (1.9 mmole), filtered through a celite pad. Extraction, evaporation and distillation gave 2-[(4-methyl-1-oxo)pentyl]furan as a brown oil (bp 65 - 77 °C, 0.1 mm Hg).

Step B. A solution of 2-[(4-methyl-1-oxo)pentyl]furan (1 mmole) in benzene was treated with ethylene glycol (2.1 mmole) and p-toluenesulfonie acid (0.05 mmole) at reflux for 60 h while removing water via a Dean-Stark trap. Triethyl orthoformate (0.6

solid was collected through filtration to give 2-amino-5-isobutyl-4-[2-(5-diethylphosphono)furanyl]thiazole.

Step C. A solution of 2-amino-5-isobutyl-4-[2-(5-diethylphosphono)-furanyl]thiazole (1 mmole) in methylene chloride was treated with bromotrimethylsilane (10 mmole) at 25 °C for 8 h. The reaction mixture was evaporated to dryness and the residue was suspended in water. The resulting solid was collected through filtration to give 2-amino-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (**3.1**) as an off-white solid. mp > 250 °C. Anal. calcd. for $C_{11}H_{15}N_2O_4PS$ + 1.25HBr: C: 32.75; H: 4.06; N: 6.94. Found: C: 32.39; H: 4.33; N: 7.18.

According to the above procedures or in some cases with minor modifications of these procedures using conventional chemistry the following compounds were prepared:

(**3.2**) 2-Methyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd. for $C_{12}H_{16}NO_4PS$ + HBr + $0.1CH_2Cl_2$: C: 37.20; H: 4.44; N: 3.58. Found: C: 37.24; H: 4.56; N: 3.30.

(**3.3**) 4-[2-(5-Phosphono)furanyl]thiazole. Anal. calcd. for $C_7H_6NO_4PS$ + 0.65 HBr: C: 29.63; H: 2.36; N: 4.94. Found: C: 29.92; H: 2.66; N: 4.57.

(**3.4**) 2-Methyl-4-[2-(5-phosphono)furanyl]thiazole. mp 235 - 236 °C. Anal. calcd. for $C_8H_8NO_4PS$ + $0.25H_2O$: C: 38..48; H: 3.43; N: 5.61. Found: C: 38.68; H: 3.33; N: 5.36.

(**3.5**) 2-Phenyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd. for $C_{17}H_{18}NO_4PS$ + HBr: C: 45.96; H: 4.31; N: 3.15. Found: C: 45.56; H: 4.26; N: 2.76.

(**3.6**) 2-Isopropyl-4-[2-(5-phosphono)furanyl]thiazole. mp 194 - 197 °C. Anal. calcd. for $C_{10}H_{12}NO_4PS$: C: 43.96; H: 4.43; N: 5.13. Found: C: 43.70; H: 4.35; N: 4.75.

(**3.7**) 5-Isobutyl-4-[2-(5-phosphono)furanyl]thiazole. mp 164 - 166 °C. Anal. calcd. for $C_{11}H_{14}NO_4PS$: C: 45.99; H: 4.91; N: 4.88. Found: C: 45.63; H: 5.01; N: 4.73.

(**3.8**) 2-Aminothiocarbonyl-4-[2-(5-phosphono)furanyl]thiazole. mp 189 - 191 °C. Anal. calcd. for $C_8H_7N_2O_4PS_2$: C: 33.10; H: 2.43; N: 9.65. Found: C: 33.14; H: 2.50; N: 9.32.

(**3.9**) 2-(1-Piperidyl)-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd. for $C_{16}H_{23}N_2O_4PS$ + 1.3HBr: C: 40.41; H: 5.15; N: 5.89. Found: C: 40.46; H: 5.36; N: 5.53.

(**3.10**) 2-(2-Thienyl)-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd. for

$C_{10}H_{13}N_2O_4PS$ + 1HBr: C: 32.53; H: 3.82; N: 7.59. Found: C: 32.90; H: 3.78; N: 7.65.

(3.21) 2-Amino-5-ethyl-4-[2-(5-phosphono)furanyl]thiazole. mp > 250 °C. Anal. calcd. for $C_9H_{11}N_2O_4PS$: C: 39.42; H: 4.04; N: 10.22. Found: C: 39.02; H: 4.15; N: 9.92.

(3.22) 2-Cyanomethyl-4-[2-(5-phosphono)furanyl]thiazole. mp 204 - 206 °C. Anal. calcd. for $C_9H_7N_2O_4PS$: C: 40.01; H: 2.61; N: 10.37. Found: C: 39.69; H: 2.64; N: 10.03.

(3.23) 2-Aminothiocarbonylamino-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. mp 177 - 182 °C. Anal. calcd. for $C_{12}H_{16}N_3O_4PS_2$ + 0.2hexane + 0.3HBr: C: 39.35; H: 4.78; N: 10.43. Found: C: 39.61; H: 4.48; N: 10.24.

(3.24) 2-Amino-5-propyl-4-[2-(5-phosphono)furanyl]thiazole. mp 235-237 °C. Anal. calcd. for $C_{10}H_{13}N_2O_4PS$ + 0.3H_2O: C: 40.90; H: 4.67; N: 9.54. Found: C: 40.91; H: 4.44; N: 9.37.

(3.25) 2-Amino-5-ethoxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole. mp 248-250 °C. Anal. calcd. for $C_{10}H_{11}N_2O_6PS$ + 0.1HBr: C: 36.81; H: 3.43; N: 8.58. Found: C: 36.99; H: 3.35; N: 8.84.

(3.26) 2-Amino-5-methylthio-4-[2-(5-phosphono)furanyl]thiazole. mp 181-184 °C. Anal. calcd. for $C_8H_9N_2O_4PS_2$ + 0.4H_2O: C: 32.08; H: 3.30; N: 9.35. Found: C:32.09; H: 3.31; N: 9.15.

(3.27) 2-Amino-5-cyclopropyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd. for $C_{10}H_{11}N_2O_4PS$ + 1H_2O + 0.75HBr: C: 32.91; H: 3.80; N: 7.68. Found: C: 33.10; H: 3.80; N: 7.34.

(3.28) 2-Amino-5-methanesulfinyl-4-[2-(5-phosphono)furanyl]thiazole. mp > 250 °C. Anal. calcd. for $C_8H_9N_2O_5PS_2$ + 0.35NaCl: C: 29.23; H: 2.76; N: 8.52. Found: C: 29.37; H: 2.52; N: 8.44.

(3.29) 2-Amino-5-benzyloxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{15}H_{13}N_2O_6PS$ + 0.2H_2O: C: 46.93; H: 3.52; N: 7.30. Found: C: 46.64; H: 3.18; N: 7.20.

(3.30) 2-Amino-5-cyclobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{11}H_{13}N_2O_4PS$ + 0.15 HBr + 0.15H_2O: C: 41.93; H: 4.30; N: 8.89. Found: C: 42.18; H: 4.49; N: 8.53.

(3.31) 2-Amino-5-cyclopropyl-4-[2-(5-phosphono)furanyl]thiazole hydrobromide. Anal. calcd for $C_{10}H_{11}N_2O_4PSBr$ + 0.73HBr + 0.15MeOH + 0.5H_2O: C: 33.95; H: 3.74; N: 7.80;

S: 8.93; Br: 16.24. Found: C: 33.72; H: 3.79; N: 7.65; S: 9.26; Br: 16.03.

(**3.32**) 2-Amino-5-[(N,N-dimethyl)aminomethyl]-4-[2-(5-phosphono)furanyl]thiazole dihydrobromide. Anal. calcd for $C_{10}H_{16}N_3O_7Br_2PS$+ $0.8CH_2Cl_2$: C: 24.34; H: 3.33; N: 7.88. Found: C: 24.23; H: 3.35; N: 7.64.

(**3.33**) 2-Amino-5-methoxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole. Mp 227 °C (decomp). Anal. calcd for $C_9H_9N_2O_6PS$ + $0.1H_2O$ + 0.2HBr: C: 33.55; H: 2.94; N: 8.69. Found: C: 33.46; H: 3.02; N: 8.49.

(**3.34**) 2-Amino-5-ethylthiocarbonyl-4-[2-(5-phosphono)furanyl]thiazole . Mp 245 °C (decomp). Anal. calcd for $C_{10}H_{11}N_2O_5PS_2$: C: 35.93; H: 3.32; N: 8.38. Found: C: 35.98; H: 3.13; N: 8.17.

(**3.35**) 2-Amino-5-propyloxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole . Mp 245 °C (decomp). Anal. calcd for $C_{11}H_{13}N_2O_6PS$: C: 39.76; H: 3.94; N: 8.43. Found: C: 39.77; H: 3.72; N: 8.19.

(**3.36**) 2-Amino-5-benzyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{14}H_{13}N_2O_4PS$ +H_2O: C: 47.46; H: 4.27; N: 7.91. Found: C: 47.24; H: 4.08; N: 7.85.

(**3.37**) 2-Amino-5-[(N,N-diethyl)aminomethyl]-4-[2-(5-phosphono)furanyl]thiazole dihydrobromide. Anal. calcd for $C_{12}H_{20}N_3O_4Br_2PS$ + 0.1HBr + 1.4 MeOH : C: 29.47; H: 4.74; N: 7.69. Found: C: 29.41; H: 4.60; N: 7.32.

(**3.38**) 2-Amino-5-[(N,N-dimethyl)carbamoyl]-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{10}H_{12}N_3O_5PS$ + 1.3HBr + $1.0H_2O$ + 0.3 Acetone: C: 28.59; H: 3.76; N: 9.18. Found: C: 28.40; H: 3.88; N: 9.01.

(**3.39**) 2-Amino-5-carboxyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_8H_7N_2O_6PS$ + 0.2HBr + 0.1 H_2O : C: 31.18; H: 2.42; N: 9.09. Found: C: 31.11; H: 2.42; N: 8.83.

(**3.40**) 2-Amino-5-isopropyloxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole . Mp 240 °C (decomp). Anal. calcd for $C_{11}H_{13}N_2O_6PS$: C: 39.76; H: 3.94; N: 8.43. Found: C: 39.42; H: 3.67; N: 8.09.

(**3.41**) 2-Methyl-5-ethyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{10}H_{12}O_4PNS$ + 0.75HBr + $0.35H_2O$: C: 36.02; H: 4.13; N: 4.06. Found: C: 36.34; H: 3.86; N: 3.69.

(**3.42**) 2-Methyl-5-cyclopropyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for

$C_{11}H_{12}NO_4PS + 0.3HBr + 0.5CHCl_3$: C: 37.41; H: 3.49; N: 3.79. Found: C: 37.61; H: 3.29; N: 3.41.

(**3.43**) 2-Methyl-5-ethoxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{11}H_{12}NO_6PS$: C: 41.64; H: 3.81; N: 4.40. Found: C: 41.61; H: 3.78; N: 4.39.

(**3.44**) 2-[(N-acetyl)amino]-5-methoxymethyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{11}H_{13}N_2O_6PS + 0.15HBr$: C: 38.36; H: 3.85; N: 8.13. Found: C: 38.74; H: 3.44; N: 8.13.

(**3.45**) 2-Amino-5-(4-morpholinyl)methyl-4-[2-(5-phosphono)furanyl]thiazole dihydrobromide. Anal. calcd for $C_{12}H_{18}Br_2N_3O_5PS + 0.25HBr$: C: 27.33; H: 3.49; N: 7.97. Found: C: 27.55; H: 3.75; N: 7.62.

(**3.46**) 2-Amino-5-cyclopropylmethoxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole. Mp 238 °C (decomp). Anal. calcd for $C_{12}H_{13}N_2O_6PS$: C: 41.86; H: 3.81; N: 8.14. Found: C: 41.69; H: 3.70; N: 8.01.

(**3.47**) 2-Amino-5-methylthio-4-[2-(5-phosphono)furanyl]thiazole N,N-dicyclohexylammonium salt. Mp >250 °C. Anal. calcd for $C_8H_9N_2O_4PS_2 + 1.15\ C_{12}H_{23}N$: C: 52.28; H: 7.13; N: 8.81. Found: C: 52.12; H: 7.17; N: 8.81.

(**3.48**) 2-[(N-Dansyl)amino]-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{23}H_{26}N_3O_6PS_2 + 0.5HBr$: C: 47.96; H: 4.64; N: 7.29. Found: C: 48.23; H: 4.67; N: 7.22.

(**3.49**) 2-Amino-5-(2,2,2-trifluoroethyl)-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_9H_8N_2F_3O_4PS$: C:32.94, H:2.46, N:8.54. Found: C:32.57, H:2.64, N:8.14.

(**3.50**) 2-Methyl-5-methylthio-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_9H_{10}NO_4PS_2$: C: 37.11; H: 3.46; N: 4.81. Found: C: 36.72; H: 3.23; N: 4.60.

(**3.51**) 2-Amino-5-methylthio-4-[2-(5-phosphono)furanyl]thiazole ammonium salt. Anal. calcd for $C_8H_{12}N_3O_4PS_2$: C: 31.07; H: 3.91; N: 13.59. Found: C: 31.28; H: 3.75; N: 13.60.

(**3.52**) 2-Cyano-5-ethyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{10}H_9N_2O_4PS$: C: 42.26; H: 3.19; N: 9.86. Found: C: 41.96; H: 2.95; N: 9.76.

(**3.53**) 2-Amino-5-hydroxymethyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_8H_9N_2O_5PS$: C: 34.79; H: 3.28; N: 10.14. Found: C: 34.57; H: 3.00; N: 10.04.

(**3.54**) 2-Cyano-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{12}H_{13}N_2O_4SP + 0.09HBr$: C: 46.15; H: 4.20; N: 8.97. Found: C: 44.81; H: 3.91; N: 8.51.

(**3.55**) 2-Amino-5-isopropylthio-4-[2-(5-phosphono)furanyl]thiazole hydrobromide. Anal. calcd for $C_{10}H_{14}BrN_2O_4PS_2$: C: 29.94; H: 3.52; N: 6.98. Found: C: 30.10; H: 3.20; N: 6.70.

(**3.56**) 2-Amino-5-phenylthio-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{13}H_{11}N_2O_4PS_2$: C: 44.07; H: 3.13; N: .91. Found: C: 43.83; H: 3.07; N: 7.74.

(**3.57**) 2-Amino-5-tert-butylthio-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{11}H_{15}N_2O_4PS_2 + 0.6CH_2Cl_2$: C: 36.16; H: 4.24; N: 7.27. Found: C: 36.39; H: 3.86; N: 7.21.

(**3.58**) 2-Amino-5-propylthio-4-[2-(5-phosphono)furanyl]thiazole hydrobromide. Anal. calcd for $C_{10}H_{14}BrN_2O_4PS_2$: C: 29.94; H: 3.52; N: 6.98. Found: C: 29.58; H: 3.50; N: 6.84.

(**3.59**) 2-Amino-5-ethylthio-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_9H_{11}N_2O_4PS_2 + 0.25HBr$: C: 33.11; H: 3.47; N: 8.58. Found: C: 33.30; H: 3.42; N: 8.60.

(**3.60**) 2-[(N-tert-butyloxycarbonyl)amino]-5-methoxymethyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{14}H_{19}N_2O_7PS$: C: 43.08; H: 4.91; N: 7.18. Found: C: 42.69; H: 4.58; N: 7.39.

(**3.61**) 2-Hydroxyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_7H_6NO_5PS$: C: 34.02; H: 2.45; N: 5.67. Found: C: 33.69; H: 2.42; N: 5.39.

(**3.62**) 2-Hydroxyl-5-ethyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_9H_{10}NO_5PS$: C: 39.28; H: 3.66; N: 5.09. Found: C: 39.04; H: 3.44; N: 4.93.

(**3.63**) 2-Hydroxyl-5-isopropyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{10}H_{12}NO_5PS + 0.1HBr$: C: 40.39; H: 4.10; N: 4.71. Found: C: 40.44; H: 4.11; N: 4.68.

(**3.64**) 2-Hydroxyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{11}H_{14}NO_5PS$: C: 43.57; H: 4.65; N: 4.62. Found: C: 43.45; H: 4.66; N: 4.46.

(**3.65**) 5-Ethoxycarbonyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_{10}H_{10}NO_6PS$: C: 39.61; H: 3.32; N: 4.62. Found: C: 39.60; H: 3.24; N: 4.47.

(**3.66**) 2-Amino-5-vinyl-4-[2-(5-phosphono)furanyl]thiazole. Anal. calcd for $C_9H_9N_2O_4PS + 0.28HCl$: C: 37.66; H: 3.26; N: 9.46. Found: C: 37.96; H: 3.37; N: 9.10.

(**3.67**) 2-Amino-4-[2-(6-phosphono)pyridyl]thiazole hydrobromide.

acetate (1.4 mmole), 3,4-butanedione (3 mmole) and isobutylamine (3 mmole) in glacial acetic acid was heated at 100 °C for 24 h. Evaporation and chromatography gave 4,5-dimethyl-1-isobutyl-2-[2-(5-diethylphosphono)furanyl]imidazole as an yellow solid.

Step I. 4,5-Dimethyl-1-isobutyl-2-[2-(5-diethylphosphono)furanyl]-imidazole was subjected to Step C of Example 3 to give 4,5-dimethyl-1-isobutyl-2-[2-(5-phosphono)furanyl]imidazole (**5.23**); Anal. Calcd. for $C_{13}H_{19}N_2O_4P$ + 1.35HBr: C: 38.32; H: 5.03; N: 6.87. Found: C: 38.09; H: 5.04; N: 7.20.

According to the above procedures or in some cases with some minor modifications of the above procedures, the following compounds were prepared:

(**5.2**) 2-Amino-5-propyl-4-[2-(5-phosphono)furanyl]oxazole. mp 250 °C (decomp.); Anal. Calcd. for $C_{10}H_{13}N_2O_5P$: C: 44.13; H: 4.81 ; N: 10.29. Found: C: 43.74; H: 4.69; N: 9.92.

(**5.3**) 2-Amino-5-ethyl-4-[2-(5-phosphono)furanyl]oxazole. Anal. Calcd. for $C_9H_{11}N_2O_5P$ + 0.4H_2O: C: 40.73; H: 4.48 ; N: 10.56. Found: C: 40.85; H: 4.10 ; N: 10.21.

(**5.4**) 2-Amino-5-methyl-4-[2-(5-phosphono)furanyl]oxazole. Anal. Calcd. for $C_8H_9N_2O_5P$ + 0.1H_2O: C: 39.07 ; H: 3.77 ; N: 11.39. Found: C: 38.96; H: 3.59; N: 11.18.

(**5.5**) 2-Amino-4-[2-(5-phosphono)furanyl]oxazole. Anal. Calcd. for $C_7H_7N_2O_5P$ + 0.6H_2O: C: 34.90; H: 3.43 ; N: 11.63. Found: C: 34.72; H: 3.08 ; N: 11.35.

(**5.6**) 2-Amino-5-isobutyl-4-[2-(5-phosphono)furanyl]oxazole hydrogen bromide. Anal. Calcd. for $C_{11}H_{16}N_2O_5BrP$ + 0.4H_2O: C: 35.29; H: 4.52 ; N: 7.48. Found: C: 35.09; H: 4.21 ; N: 7.34.

Example 6.

A. Preparation of various phosphoramides as prodrugs

Step A. A suspension of 2-methyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (1 mmole) in thionyl chloride (5 mL) was warmed at reflux for 4 h. The cooled reaction mixture was evaporated to dryness and the resulting yellow residue was dissolved in methylene chloride and treated with a solution of the corresponding benzyl alcohol (4 mmole) and pyridine (2.5 mmole) in methylene chloride. After stirring at 25 °C for 24 h

the reaction mixture was subjected to extraction and chromatography to give the titled compounds.

Step B. A solution of 2-methyl-5-isopropyl-4-[2-(5-phosphono)-furanyl]thiazole dichloridate (generated as in Step A) (1 mmole) in dichloromethane (5 mL) was cooled to 0 °C and treated with a solution of benzyl alcohol (0.9 mmole) in dichloromethane (0.5 mL) and pyridine (0.3 mL). The resulting reaction solution was stirred at 0 °C for 1h, and then added a solution of ammonia (excess) in THF. After stirring at room temperature for 16 h, the reaction was evaporated to dryness and the residue was purified by chromatography to give 2-methyl-5-isopropyl-4-[2-(5-phosphonomonoamido)furanyl]thiazole (**6.1**) as a yellow hard gum and 2-methyl-5-isopropyl-4-[2-(5-phosphorodiamido)furanyl]-thiazole (**6.2**) as a yellow hard gum.
(**6.1**) 2-Methyl-5-isopropyl-4-[2-(5-phosphonomonoamido)furanyl]thiazole: MS *m/e* 299 (M-H).
(**6.2**) 2-Methyl-5-isopropyl-4-[2-(5-phosphorodiamido)furanyl]thiazole: MS *m/e* 298 (M-H).

Alternatively, a different method was used to prepare other phosphoramides as exemplified in the following procedure:

Step C. A suspension of 2-amino-5-methylthio-4-[2-(5-phosphono)furanyl]-thiazole dichloridate (generated as in Step A) (1 mmole) in dichloromethane (5 mL) was cooled to 0 °C and ammonia (excess) was bubbled through the reaction for 10 min. After stirring at room temperature for 16 h, the reaction was evaporated to dryness and the residue was purified by chromatography to give 2-amino-5-methylthio-4-[2-(5-phosphorodiamido)furanyl]thiazole (**6.3**) as a foam. Anal. Calcd for $C_8H_{11}N_4O_2PS_2$ + 1.5 HCl + 0.2 EtOH: C: 28.48; H: 3.90; N: 15.82. Found: C: 28.32; H: 3.76; N: 14.21.

The following compounds were prepared according to the above described procedures or in some cases with minor modifications of these procedures:
(**6.4**) 2-Amino-5-isobutyl-4-[2-(5-phosphonomonoamido)furanyl]thiazole. Mp 77 –81 °C. Anal. Calcd for $C_{11}H_{16}N_3O_3PS$ + H_2O + 0.8 Et_3N: C: 47.41; H: 7.55; N: 13.30. Found: C: 47.04; H: 7.55; N: 13.67.

methyl ester hydrochloride (1.2 mmole) in pyridine (0.8 mL) and dichloromethane (3 mL) at 0 °C. The resulting reaction solution was stirred at room temperature for 14 h. Evaporation and chromatography gave 2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1-methoxycarbonyl)ethyl)phosphonamido]-furanyl}thiazole **(6.6)** as an oil. Anal. calcd. for $C_{21}H_{26}N_3O_5PS$: C: 54.42; H: 5.65; N: 9.07. Found: C: 54.40; H: 6.02; N: 8.87.

The following compounds were prepared according to the above described procedures:

(6.7) 2-amino-5-isobutyl-4-{2-[5-(O-phenylphosphonamido)]furanyl}thiazole. mp 205 °C (decomp). Anal. calcd. for $C_{17}H_{20}N_3O_3PS + 0.3\ H_2O + 0.3$ HCl: C: 51.86; H: 5.35; N: 10.67. Found: C: 51.58; H: 4.93; N: 11.08.

(6.8) 2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-ethoxycarbonylmethyl)-phosphonamido]furanyl}thiazole. Anal. calcd. for $C_{21}H_{26}N_3O_5PS$: C: 54.42; H: 5.65; N: 9.07. Found: C: 54.78; H: 5.83; N: 8.67.

(6.9) 2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-isobutyl)phosphonamido]-furanyl}thiazole. mp 151 - 152 °C. Anal. calcd. for $C_{21}H_{28}N_3O_3PS$: C: 58.18; H: 6.51; N: 9.69. Found: C: 58.12; H: 6.54; N: 9.59.

(6.18) 2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1-(1-ethoxycarbonyl-2-phenyl)-ethyl)phosphonamido)]furanyl}thiazole. Anal. calcd. for $C_{28}H_{32}N_3O_5PS$: C: 60.75; H: 5.83; N: 7.59. Found: C: 60.35; H: 5.77; N: 7.37.

(6.19) 2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1-(1-ethoxycarbonyl-2-methyl)-propyl)phosphonamido)]furanyl}thiazole. Anal. calcd. for $C_{23}H_{30}N_3O_5PS$: C: 56.20; H: 6.15; N: 8.55. Found: C: 55.95; H: 5.80; N: 8.35.

(6.20) 2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1-(1,3-bis(ethoxycarbonyl) propyl)phosphonamido)]furanyl}thiazole. Anal. calcd. for $C_{26}H_{34}N_3O_7PS + 0.2\ CH_2Cl_2$: C: 54.20; H: 5.97; N: 7.24. Found C: 54.06; H: 5.68; N: 7.05.

(6.21) 2-amino-5-isobutyl-4-{2-[5-(O-(3-chlorophenyl)- N-(1-(1-methoxy-carbonyl)ethyl) propyl)phosphonamido)]furanyl}thiazole. Anal. caled. for $C_{21}H_{25}N_3O_5PSCl$: C: 50.65; H: 5.06; N: 8.44. Found: C: 50.56; H: 4.78; N: 8.56.

(**6.11**) 2-Methyl-5-isobutyl-4-{2-[5-(1-phenyl-1,3-propyl)phosphonamido]-furanyl}-thiazole major isomer. Anal. calcd. for $C_{21}H_{25}N_2O_3PS + 0.25\ H_2O$: C: 59.91; H: 6.11; N: 6.65. Found: C: 60.17; H: 5.81; N: 6.52.

(**6.12**) 2-Amino-5-isobutyl-4-{2-[5-(1-phenyl-1,3-propyl)phosphonamido]-furanyl}-thiazole major isomer. Anal. calcd. for $C_{20}H_{24}N_3O_3PS + 0.25\ H_2O + 0.1\ CH_2Cl_2$: C: 55.27; H: 5.72; N: 9.57. Found: C: 55.03; H: 5.42; N: 9.37.

(**6.13**) 2-Amino-5-isobutyl-4-{2-[5-(1-phenyl-1,3-propyl)phosphonamido]-furanyl}-thiazole minor isomer. Anal. calcd. for $C_{20}H_{24}N_3O_3PS + 0.15\ CH_2Cl_2$: C: 56.26; H: 5.69; N: 9.77. Found: C: 56.36; H: 5.46; N: 9.59.

(**6.14**) 2-Amino-5-methylthio-4-{2-[5-(1-phenyl-1,3-propyl)phosphonamido]-furanyl}thiazole less polar isomer. Anal. calcd. for $C_{17}H_{18}N_3O_3PS_2 + 0.4$ HCl: C: 48.38; H: 4.39; N: 9.96. Found: C: 48.47; H: 4.21; N: 9.96.

(**6.15**) 2-Amino-5-methylthio-4-{2-[5-(1-phenyl-1,3-propyl)phosphonamido]-furanyl}thiazole more polar isomer. Anal. calcd. for $C_{17}H_{18}N_3O_3PS_2$: C: 50.11; H: 4.45; N: 10.31. Found: C: 49.84; H: 4.19; N: 10.13.

(**6.16**) 2-Amino-5-methylthio-4-{2-[5-(N-methyl-1-phenyl-1,3-propyl)-phosphonamido]furanyl}thiazole. Anal. calcd. for $C_{18}H_{20}N_3O_3PS_2 + 0.25$ HCl: C: 50.21; H: 4.74; N: 9.76. Found: C: 50.31; H: 4.46; N: 9.79.

(**6.17**) 2-Amino-5-methylthio-4-{2-[5-(1-phenyl-1,3-propyl)-N-acetyl-phosphonamido]furanyl}thiazole. Anal. calcd. for $C_{22}H_{26}N_3O_4PS + 1.25\ H_2O$: C: 54.82; H: 5.96; N: 8.72. Found: C: 55.09; H: 5.99; N: 8.39.

(**6.26**) 2-amino-5-isobutyl-4-{2-[5-(1-oxo-1-phospha-2-oxa-7-aza-3,4-benzocycloheptan-1-yl)]furanyl}thiazole, major isomer. Mp 233 - 234 °C. Anal. calcd. for $C_{21}H_{24}N_3O_5PS + 0.2\ CHCl_3$: C: 52.46; H: 5.03; N: 8.66. Found C: 52.08; H: 4.65; N: 8.58.

(**6.27**) 2-amino-5-isobutyl-4-{2-[5-(1-oxo-1-phospha-2-oxa-7-aza-3,4-benocycloheptan-1-yl)]furanyl}thiazole, minor isomer. MS calcd. for $C_{21}H_{24}N_3O_5PS$ + H: 462, found 462.

(**6.34**) 2-amino-5-isobutyl-4-{2-[5-(3-(3,5-dichlorophenyl)-1,3-propyl)phosphonamido]furanyl}thiazole. Anal. calcd. for $C_{20}H_{22}N_3O_3PSCl_2$: C: 49.39; H: 4.56; N: 8.64. Found: C: 49.04; H: 4.51; N: 8.37.

(6.35) 2-amino-5-isobutyl-4-{2-[5-(4,5-benzo-1-oxo-1-phospha-2-oxa-6-aza)cyclohexan-1-yl]furanyl}thiazole. Anal. calcd. for $C_{18}H_{20}N_3O_3PS + 0.7\ H_2O$: C; 53.78; H: 5.37; N: 10.45. Found C: 53.63; H: 5.13; N: 10.36.

Section 2.
Synthesis of Compounds of Formula X

Example 7.

Preparation of 2-amino-4-phosphonomethyloxy-6-bromobenzothiazole.

Step A. A solution of $AlCl_3$ (5 mmole) in EtSH (10 mL) was cooled to 0 °C and treated with 2-amino-4-methoxybenzothiazole (1 mmole). The mixture was stirred at 0-5 °C for 2 h. Evaporation and extraction gave 2-amino-4-hydroxybenzothiazole as white solid.

Step B. A mixture of 2-amino-4-hydroxybenzothiazole (1 mmole) and NaH (1.3 mmole) in DMF (5 mL) was stirred at 0 °C for 10 min, and then treated with diethylphosphonomethyl trifluoromethylsulfonate (1.2 mmole). After being stirred at room temperature for 8 h, the reaction was subjected to extraction and chromatography to give 2-amino-4-diethylphosphonomethyloxybenzothiazole as an oil.

Step C. A solution of 2-amino-4-(diethylphosphonomethyloxy)benzothiazole (1 mmole) in AcOH (6 mL) was cooled to 10 °C and treated with bromine (1.5 mmole) in AcOH (2 mL). After 5 min the mixture was stirred at room temperature for 2.5 h. The yellow precipitate was collected via filtration and washed with CH_2Cl_2 to give 2-amino-4-diethylphosphonomethyloxy-6-bromobenzothiazole.

Step D. A solution of 2-amino-4-diethylphosphonomethyloxy-6-bromobenzothiazole (1 mmole) in CH_2Cl_2 (4 mL) was treated with TMSBr (10 mmole) at 0 °C. After stirred for 8 h at room temperature the reaction was evaporated to dryness and the residue was taken into water (5 mL). The resulting precipitate was collected via filtration and washed with water to give 2-amino-4-phosphonomethyloxy-6-bromobenzothiazole (**7.1**) as white solid. mp >220 °C(dec.). Anal. Calcd. for $C_8H_8N_2O_4PSBr$: C:28.34; H:2.38; N:8.26. Found: C:28.32; H:2.24; N:8.06.

Similarly, the following compounds were prepared according to the above described procedures:

(**7.2**) 2-Amino-4-phosphonomethyloxybenzothiozole. mp >250 °C. Anal. Calcd. for

(11.2) 2-Amino-5-isobutyl-4-[2-(5-N,N'-bis(L-alanine acid dibenzyl ester)phosphonoamido)furanyl]thiazole. Anal. cald. For $C_{31}H_{37}N_4O_6PS$: C: 59.60; H: 5.97; N: 8.97. Found: C: 59.27; H: 5.63; N: 8.74.

(11.3) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis(benzyloxycarbonylmethyl) phosphonodiamido]furanyl}thiazole. Anal. cald. for $C_{19}H_{25}N_4O_6PS$ + 0.3 CH_2Cl_2: C: 46.93; H: 5.22; N: 11.34. Found: C: 46.92; H: 5.00; N: 11.22.

(11.4) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis(benzyloxycarbonylmethyl) phosphonodiamido]furanyl}thiazole. Anal. cald. For $C_{29}H_{33}N_4O_6PS$: C: 58.38; H: 5.57; N: 9.39. Found: C: 58.20; H: 5.26; N: 9.25.

(11.5) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis((R)-1-methoxycarbonyl)ethyl) phosphonamido]furanyl}thiazole. Anal. cald. for $C_{19}H_{29}N_4O_6PS$ + 0.6 CH2Cl2: C: 44.97; H: 5.82; N: 10.70. Found: C: 44.79; H: 5.46; N: 10.48.

(11.6) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis((S)-1-ethoxycarbonyl)ethyl) phosphonamido]furanyl}thiazole. mp. 164-165 ºC: Anal. cald. for $C_{21}H_{33}N_4O_6PS$ + 0.61 CH_2Cl_2: C: 46.99; H: 6.24; N: 10.14. Found: C: 47.35; H: 5.85; N: 9.85.

(11.7) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis((t-butoxycarbonyl)methyl) phosphonamido]furanyl}thiazole. Anal. cald. for $C_{23}H_{37}N_4O_6PS$ + 0.15 CH_2Cl_2: C: 51.36; H: 6.94; N: 10.35. Found: C: 51.34; H: 6.96; N: 10.06.

(11.8) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis(ethoxycarbonyl) methyl)phosphonamido)]furanyl}thiazole. Anal. cald. for $C_{19}H_{29}N_4O_6PS$ + 0.1 EtOAc + 0.47 CH_2Cl_2: C: 45.79; H: 5.94; N: 10.75. Found: C: 46.00; H: 5.96; N: 10.46.

(11.9) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis (1-methyl-1-ethoxycarbonyl)ethyl)phosphonamido]furanyl}thiazole. mp. 142-145 ºC:; Anal. cald. for $C_{23}H_{37}N_4O_6PS$: C: 52.26; 7.06; 10.60. Found: C: 52.21; 6.93; 10.62.

(11.10) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis(ethoxycarbonylmethyl) -N,N'-dimethylphosphonamido)]furanyl}thiazole. Anal. cald. for $C_{21}H_{33}N_4O_6PS$: C: 50.39; H: 6.65; N: 11.19. Found: C: 50.57; H: 6.56; N: 11.06.

(11.11) 2-Amino-5-isobutyl-4-{2-[5-(N,N'-bis((S)-1-benzyloxycarbonyl-2-methyl)propyl) phosphonamido]furanyl}thiazole. Anal. cald. for $C_{35}H_{45}N_4O_6PS$ + 0.5 H_2O: C: 60.94; H: 6.72; N: 8.12. Found: C: 61.01: H: 6.48; N: 7.82.

Alternatively, compound **11.6** was prepared using a modified procedure. A slurry of compound **3.1** (1 mmol), oxalyl chloride (3.2 mmol) and DMF (1.1 mmol) in anhydrous toluene was heated to reflux for 1 hr. The resulting solutin was concentrated under reduced pressure to 80% of the original volume, cooled to 0°C, and trichylamine (3 mmol) and L-alanine ethyl ester (2.2 mmol) were added. The mixture was then stirred at 0°C for 2 hr. and at room temperture for 6 hr. Acetic acid (9.5 mmol) and ethanol (21 mmol) were added to the reaction mixture, and the resulting mixture was heated to reflux for 16 hr. Extraction and crystallization gave compound **11.6** as an off-white solid.

Example 12.

General procedure for mixed bis-phosphoroamidate prodrugs

To a solution of crude dichloridate (1 mmol, prepared as described in Example 40) in 5 mL of dry CH_2Cl_2 was added amine (1 mmol) followed by 4-dimethylaminopyridine (3 mmol) at 0 °C . The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was cooled back to 0 °C before adding aminoacid ester (2 mmol) and left at room temperature for 16 h. The reaction mixture was subjected to aq. work up and the mixed bis-phosphoroamidate prodrug was purified by column chromatography.

The following compounds were prepared in this manner.

(12.1) 2-Amino-5-isobutyl-4-{2-[5-(N-morpholino-N'-(1-methyl-1-ethoxycarbonyl)ethyl)-phosphonamido]furanyl}thiazole. mp. 182-183 °C: Anal. cald. for $C_{21}H_{33}N_4O_5PS$: C: 52.05; H: 6.86; N: 11.56. Found: C: 51.66; H:6.68; N: 11.31.

(12.2) 2-Amino-5-isobutyl-4-{2-[5-(N-pyrrolidino-N'-(1-methyl-1-ethoxycarbonyl)ethyl)-phosphonamido]furanyl}thiazole. mp. 189-190 °C: Anal. cald. for $C_{21}H_{33}N_4O_4PS$: C: 53.83; H: 7.10; N: 11.96. Found: C: 54.15; H: 7.48; N: 12.04.

methyl-4-chloro-2-iodobenzene-1-sulfonamide (for **13.06**); N^1-methyl-2-iodobenzene-1-sulfonamide (for **13.07**); N^1-propyl-4-chloro-2-iodobenzene-1-sulfonamide (for **(13.08)**; 2-iodophenol (for **13.09**); 5-iodo-m-xylene (for **13.10**); 1-bromo-3-iodobenzene (for **13.11**); 4-iodoaniline (for **13.12**); 2,5-dimethoxy-4-iodochlorobenzene (for **13.13**); N^1-(4-chlorobenzyl)-2-iodobenzamide (for **13.14**); N^1-(4-chlorophenethyl)-2-iodobenzamide (for **13.15**); N1-benzyl-2-iodobenzene-1-sulfonamide (for **13.16**); 2-iodobenzenesulfonamide (for **13.17**); 1-iodo-2,3,4,5,6-pentamethylbenzene (for **13.18**); 3-iodophthalic acid (iodoethane and diisopropylamine included in Step C, for 13.19); 4-iodo-2-methylacetanilide (for **13.20**); 3,5-dichloro-2-iodotoluene (for **13.21**); methyl 5-hydroxy-2-iodobenzoate (for **13.22**); 2-iodo-5-methylbenzamide (for **13.23**); 5-hydroxy-2-iodobenzoic acid (iodoethane and diisopropylamine included in Step C, for 13.24); 1-iodo-4-nitrobenzene (for **13.25**); N1-(2,4-difluorophenyl)-2-iodobenzamide (for **13.26**); 3,5-dichloro-1-iodobenzene (13.27); 3-iodophenol (for **13.28**); 3-bromo-5-iodobenzoic acid (for **13.29**); 3-bromo-4,5-dimethoxybenzaldehyde (for **13.30**); 1-iodo-2-nitrobenzene (for **13.31**); 2-iodobiphenyl (for **13.32**); 2-iodobenzoic acid (iodoethane and diisopropylamine included in Step C, for 13.33); 1-bromo-4-iodobenzene (for **13.34**); 3'-bromopropiophenone (for **13.35**); 3-bromo-4-methoxybenzonitrile (for **13.36**); 1-ethyl-2-iodobenzene (for **13.37**); 2-bromo-3-nitrotoluene (for **13.38**); 4-iodoacetanilide (for **13.39**); 2,3,4,5-tetramethyliodobenzene (for **13.40**); 3-bromobiphenyl (for **13.41**); 4-chloro-2-iodobenzenesulfonamide (for **13.42**); N1-(4-iodophenyl)-2-tetrahydro-1H-pyrrol-1-ylacetamide (for **13.43**); 3,4-dimethyliodobenzene (for **13.44**); 2,4-dinitroiodobenzene (for **13.45**); 3-iodobenzylamine (for **13.46**); 2-fluoro-4-iodoaniline (for **13.47**); 3-iodobenzyl alcohol (for **13.48**); 2-bromo-1-iodobenzene (for **13.49**); 2-bromophenethyl alcohol (for **13.50**); 4-iodobenzamide (for **13.51**); 4-bromobenzonitrile (for **13.52**); 3-bromobenzonitrile (for **13.53**); 2-bromobenzonitrile (for **13.54**); 4-bromo-2-nitroaniline (for **13.55**); 2-iodoisopropylbenzene (for **13.56**); 6-amino-2-chloro-3-bromopyridine (derived from reaction of 6-amino-2-chlorobenzene (1 mmol) with bromine (1 mmol) in acetic acid (4 mL) for 2h at rt. followed by evaporation and chromatography to provide 6-amino-2-chloro-3-bromopyridine) (for **13.57**); 3-bromo-4-methylthiophene (for **13.58**); 2-bromo-4-chloroaniline (for **13.59**); 1-bromo-3-chloro-5-fluoroaniline (for **13.60**); 2-bromo-4-cyanoanisole (for **13.61**); 2-bromo-4-nitrotoluene (for **13.62**); 3-nitro-5-fluoro-1-

iodobenzene (for **13.63**); 2-iodo-4-carbomethoxyaniline (for **13.64**); 2-bromo-4-nitroanisole (for **13.65**); 2-chloro-1-iodo-5-trifluoromethylbenzene (for **13.66**) and 1-bromo-2,5-bis-(trifluoromethyl)benzene (for **13.67**).

Example 14

Preparation of 5-(4-Fluorophenyl)-2-furanphosphonic Acid (Compound no. 14.01).

1) A solution of diethyl 2-furanphosphonate (prepared as described in Step A, Example 13) (1 mmol) in 2 mL THF was cooled to –78 °C and added to a solution of lithium isopropylcyclohexylamide (LICA) (1 mmol) in 2 mL THF at –78 °C over 20 min. The resulting mixture was stirred –78 °C for 20 min and added into a solution of iodine (1 mmole) in 1 mL THF at –78 °C over 20 min. The mixture was then stirred at –78 °C for 20 min. Extraction and chromatography provided diethyl 5-iodo-2-furanphosphonate as a yellow oil.

2) A mixture of diethyl 5-iodo-2-furanphosphonate (1 mmol), 4-fluorophenylboronic acid (2 mmol), diisopropylethylamine (DIEA) (4 mmol) and bis(acetonitrile)dichloropalladium(II) (0.05 mmol) in 6 mL DMF was heated at 75 °C for 16 h. Extraction and chromatography provided diethyl 5-(4-fluorophenyl)-2-furanphosphonate as an oil.

Application of Step D, Example 13, to this material provided the title compound (no. **14.01**) as a white solid. HPLC R_t = 5.09 min; negative ion electrospray MS M-1 found: 241.

Substitution of 2,4-dichlorophenylboronic acid into this method provided compound no. **14.02**. Substitution of 3-amino-5-carbomethoxyphenylboronic acid into this method provided compound no. **14.03**.

Example 15

Preparation of 5-(4-Bromo-3-aminophenyl)-2-furanphosphonic Acid (Compound no. 15.01).

Reaction of 3-aminophenylboronic acid hydrochloride with diethyl 5-iodo-2-furanphosphonate as described in Step B of Example 14 provided diethyl 5-(3-aminophenyl)-2-furanphosphonate as an oil.

Example A: Inhibition of Human Liver FBPase

E. coli strain BL21 transformed with a human liver FBPase-encoding plasmid was obtained from Dr. M. R. El-Maghrabi at the State University of New York at Stony Brook. hlFBPase was typically purified from 10 liters of *E. coli* culture as described by M. Gidh-Jain et al. J. Biol Chem. 269, 27732-27738 (1994). Enzymatic activity was measured spectrophotometrically in reactions that coupled the formation of product (fructose 6-phosphate) to the reduction of dimethylthiazoldiphenyltetrazolium bromide (MTT) via NADP and phenazine methosulfate (PMS), using phosphoglucose isomerase and glucose 6-phosphate dehydrogenase as the coupling enzymes. Reaction mixtures (200 µL) were made up in 96-well microtitre plates, and consisted of 50 mM Tris-HCl, pH 7.4, 100 mM KCl, 5 mM EGTA, 2 mM $MgCl_2$, 0.2 mM NADP, 1 mg/ml BSA, 1 mM MTT, 0.6 mM PMS, 1 unit/mL phosphoglucose isomerase, 2 units/mL glucose 6-phosphate dehydrogenase, and 0.150 mM substrate (fructose 1,6-bisphosphate). Inhibitor concentrations were varied from 0.01 µM to 10 µM. Reactions were started by the addition of 0.002 units of pure hlFBPase and were monitored for 7 minutes at 590 nm in a Molecular Devices Plate Reader (37 °C).

The potencies of select compounds against human liver FBPase are shown in the table below:

Table 1.

Compound	IC50, µM
AMP	1.3
E	0.055
D	1.0
B	5.0
C	30
F	0.12
G	0.015
H	0.025
I	0.018

Example B: Inhibition of rat liver and mouse liver FBPase

E. coli strain BL21 transformed with a rat liver FBPase-encoding plasmid was obtained from Dr. M. R. El-Maghrabi at the State University of New York at Stony Brook, and purified as described (El-Maghrabi, M.R., and Pilkis, S.J. (1991) Biochem. Biophys. Res. Commun. 176: 137-144). Mouse liver FBPase was obtained by homogenizing freshly isolated mouse liver in 100 mM Tris-HCl buffer, pH 7.4, containing 1 mM EGTA, and 10% glycerol. The homogenate was clarified by centrifugation, and the 45-75% ammonium sulfate fraction prepared. This fraction was redissolved in the homogenization buffer and desalted on a PD-10 gel filtration column (Biorad) eluted with same. This partially purified fraction was used for enzyme assays. Both rat liver and mouse liver FBPase were assayed as described for human liver FBPase in Example A. Generally, as reflected by higher IC_{50} values, the rat and mouse liver enzymes are less sensitive to inhibition by the compounds tested than the human liver enzyme.

The following Table depicts the IC_{50} values for several compounds prepared in the Examples:

Table 2.

Compound	IC_{50} Rat Liver (μM)	IC_{50} Mouse Liver (μM)
AMP	25	15
B	140	33
D	1.25	55
C	>100	>100
E	0.4	1.1
F	2.0	
G	0.25	
H	0.175	
I	0.05	

Example C: Inhibition of Gluconeogenesis by an FBPase Inhibitor in Rat Hepatocytes

Hepatocytes were prepared from fed Sprague-Dawley rats (250-300 g) according to the procedure of Berry and Friend (Berry, M.N., Friend, D.S., 1969, J. Cell. Biol. 43, 506-520) as modified by Groen (Groen, A.K., Sips, H.J., Vervoorn, R.C., Tager, J.M. , 1982, Eur. J. Biochem. 122, 87-93). Hepatocytes (75 mg wet weight/mL) were incubated in 1 mL Krebs-bicarbonate buffer containing 10 mM Lactate, 1 mM pyruvate, 1 mg/mL

anesthetized with halothane and a liver biopsy (approx. 1 g) was taken, as well as a blood sample (2 mL) from the posterior vena cava. A heparin flushed syringe and needle was used for blood collection. The liver sample was immediately homogenized in ice-cold 10% perchloric acid (3 mL), centrifuged, and the supernatant neutralized with 1/3rd volume of 3 M KOH/3 M KH_2CO_3. Following centrifugation and filtration, the neutralized extract was analyzed for fructose 1,6-bisphosphate content as described for isolated hepatocytes in Example C. Blood glucose was measured by means of a Hemocue analyzer (Hemocue Inc, Mission Viejo, CA).

Analysis of liver metabolites revealed that Compound A was efficiently converted to Compound B, with intrahepatic levels of the latter reaching 3 μmolcs/g tissue within 1 hour. Although levels declined slowly over time, Compound B was measurable out to the final, 24 hour time point. In plasma 5-bromo-1-βD-ribofuranosyl-imidazole-carboxamide but not Compound A was detectable, suggesting that Compound A was rapidly deacetylated at all three positions.

The single 250 mg/kg dose of Compound A markedly lowered blood glucose for approximately 8 hours, at which time levels in the treated animals rebounded slowly to those of the vehicle-treated controls. Drug treatment resulted in the elevation of hepatic fructose -1,6-bisphosphate levels. The time course of elevation of this gluconeogenic intermediate correlated well with the time course of glucose lowering. Peak elevation was observed at near maximal glucose lowering, and as blood glucose levels rebounded, fructose-1,6-bisphosphate levels slowly returned to normal. The latter observations are consistent with the inhibition of gluconeogenesis by Compound A at the level of fructose-1,6-bisphosphatase.

Example F: Analysis of Hepatic and Plasma Drug Levels After Administration of Compounds D, E. F, and G intraperitoneally to Normal Fasted Rats.

Sprague-Dawley rats (250-300 g) were fasted for 18 hours and then dosed intraperitoneally either with saline or FBPase inhibitor. The vehicle used for drug administration was 10 mM bicarbonate. One hour post injection, rats were anesthetized with halothane, and liver and blood samples were taken and processed as described in Example E. The neutralized liver extracts were analyzed for FBPase inhibitor content by

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CERTIFICATE OF CORRECTION

PATENT NO. : 7,563,774

APPLICATION NO.: 09/900,364

DATED : July 21, 2009

INVENTORS : Paul D. van Poelje, Mark D. Erion, Toshihiko Fujiwara

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 6,
Lines 60-61, "-oxyalkyleneaamino-" should read -- -oxyalkyleneamino- --.

Column 7,
Line 5, "include norbomyl" should read --include norbornyl--.

Column 10,
Line 55, "Kharnnei" should read --Khamnei--.

Column 26,
Line 7, "all except H" should read --all except —H--.
Line 26, "OR^3 and" should read -- —OR^3 and--.
Line 63, "R^{16} is $-(CR^{12}R^{13})_nC(O)-R^{14}$" should read --$R^{16}$ is $-(CR^{12}R^{13})_n-C(O)-R^{14}$--.

Column 27,
Line 60, "OR^3 and" should read -- —OR^3 and--.

Column 36,
Line 50, "amnidine" should read --amidine--.
Line 52, "C_2-C_5 alkeniyl" should read --C_2-C_5 alkenyl--.

Column 37,
Line 10, "the R attached" should read --the R^1 attached--.

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 43,
Line 19, "prodrugs and salts" should read --salts or prodrugs--.

Column 46,
Line 15, "form a bidendate" should read --form a bidentate--.

Column 49,
Line 33, "A, E, and L are independently" should read --A, E, and L are selected--.

Column 51,
Line 27, "bidendate" should read --bidentate--.
Line 64, "C1-C5 alkyl or" should read --C_1-C_5 alkyl, or--.

Column 54,
Line 30, "-alkylthio-alkyl-, -alkyl-thio-," should read -- -alkylthioalkyl-, -alkylthio-,--.

Column 58,
Line 15, "are not $-NR^6$;" should read --are not $-NR^6-$;--.

Column 59,
Line 20, "Y is $-NR^6$," should read --Y is $-NR^6-$,--.

Column 62,
Line 41, "from –H, or together" should read --from –H, alkyl, or together--.
Line 42, "R^4 from a" should read --R^4 form a--.

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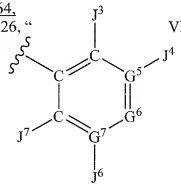
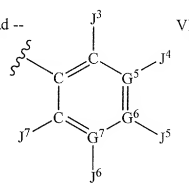
It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 64,
Lines 20-26, “  VII-6” should read --  VII-6 --.

Line 42, “alkenyl, alkylenearyl” should read --alkenyl, alkynyl, alkylenearyl--.

Column 66,
Line 22, “R" is” should read --R^{11} is--.

Column 68,
Line 48, “—$OCOR^3$, —$OCOR^3$” should read -- —$OCOR^3$, —OCO_2R^3--.

Column 69,
Line 51, “together with R^{6}” should read --together with R^{16}--.

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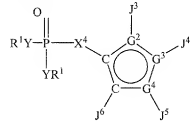
It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

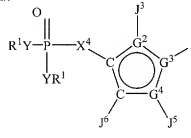
Column 70,
Line 40, "thereof.



"

should read --thereof.

In one aspect of the present invention compounds of formula VII-1 are envisioned.



--.

Line 51, "In one aspect" should read --In another aspect--.
Line 67, "formula VII-1" should read --formula VII-1-A--.

Column 72,
Line 11, "—OC_2R^3" should read -- —OCO_2R^3--.

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 73,
Line 23, "$CHR^2OC(S)OR^3$" should read -- —$CHR^2OC(S)OR^3$--.
Line 27, "SCO_2R^3" should read -- —SCO_2R^3--.
Lines 45-46, "—CH(aryl)OH, **13** $CH(CH{=}CR^2{}_2)OH$" should read
-- —CH(aryl)OH, —$CH(CH{=}CR^2{}_2)OH$--.
Line 56, "and **13** $OC(O)SR^3$" should read --and —$OC(O)SR^3$--.

Column 74,
Lines 65-66, "**13** $CHR^2OC(O)SR^3$" should read -- —$CHR^2OC(O)SR^3$--.

Column 75,
Line 25, "—CHR_2NHaryl" should read -- —CH_2NHaryl--.
Lines 33-34, "**13** OC_2R^3" should read -- —OC_2R^3--.
Line 65, "—$C(R^4)_2C(O)^3$, or" should read -- —$C(R^4)_2C(O)OR^3$, or--.

Column 76,
Lines 20-21, "aspect are compounds are such" should read
--aspect are compounds such--.

Column 85,
Lines 63-64, "7 one Y is $-NR^6$-, and the other YR^1 is $NR^{15}R^{16}$, and R^{15} is not H" should read --7 one Y is $-NR^6$–, and the other YR^1 is —$NR^{15}R^{16}$, and R^{15} is not H--.

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DATED : July 21, 2009

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 85,

Lines 65-66, "8 one Y is –NR^6–, and the other YR^1 is $NR^{15}R^{16}$," should read
--8 one Y is –NR^6–, and the other YR^1 is —$NR^{15}R^{16}$,--.

Column 86,

Lines 14-16, "10 one Y is –NR^6–, and the other YR^1 is $NR^{15}R^{16}$, and R^{16} is, where –$NR^{15}R^{16}$ is a cylic amine" should read
--10 one Y is –NR^6–, and the other YR^1 is —$NR^{15}R^{16}$, and R^{16} is, where –$NR^{15}R^{16}$ is a cylic amine--.

Lines 17-19, "11 one Y is –NR^6–, and the other YR^1 is $NR^{15}R^{16}$, where –$NR^{15}R^{16}$ is a selected from a group of morpholinyl and pyrrolidinyl" should read
--11 one Y is –NR^6–, and the other YR^1 is —$NR^{15}R^{16}$, where –$NR^{15}R^{16}$ is selected from a group of morpholinyl and pyrrolidinyl--.

Column 86,

Lines 19-20, "12 one Y is –NR^6–, and the other YR^1 is $NR^{15}R^{16}$, where –$NR^{15}R^{16}$ is a –$(CR^{12}R^{13})_n$—$C(O)R^{14}$" should read
--12 one Y is –NR^6–, and the other YR^1 is —$NR^{15}R^{16}$, where –$NR^{15}R^{16}$ is a –$(CR^{12}R^{13})_n$—$C(O)R^{14}$--.

Line 44, "$OCOR^3$," should read -- —$OCOR^3$,--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,563,774

APPLICATION NO.: 09/900,364

DATED : July 21, 2009

INVENTORS : Paul D. van Poelje, Mark D. Erion, Toshihiko Fujiwara

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 87,
Line 15, "—OR^2, R^2" should read -- —OR^2, —R^2--.

Column 96,
Lines 53-54, "groups are O—" should read --groups are —O— --.

Column 101,
Line 61, "Bis-[4-(1-triazolophenyl) esters;" should read
--Bis-[4-(1-triazolophenyl)] esters;--.

Column 104,
Line 4, "Bis-(phenyloxycarbonyloxyrnethyl) esters;" should read
--Bis-(phenyloxycarbonyloxymethyl) esters;--.

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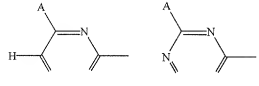
It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 105,

Line 9, "of formula" should read --of formula I-A.--.

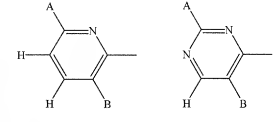
Lines 66-67, Group 2 structures,

" 3 4 "



should read

-- 3 4 --.



Column 106,

Line 36, "5. —NH—CH(CH(CH$_3$)$_2$))—C(O)R^{14}" should read
--5. —NH—CH(CH(CH$_3$)$_2$)—C(O)R^{14}--.

Line 37, "6. —NH—CH(CH$_2$(CH(CH$_3$)$_2$)))—C(O)R^{14}" should read
--6. —NH—CH(CH$_2$(CH(CH$_3$)$_2$))—C(O)R^{14}--.

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Column 107,
Line 1, "4. —NH—$CH(CH_2CoNH_2)$—$C(O)R^{14}$" should read
--4. —NH—$CH(CH_2CONH_2)$—$C(O)R^{14}$--.

Column 108,
Line 55, "4. —N—$C(CH_3)_2CH_2$—$C(O)R^{14}$" should read
--4. —NH—$C(CH_3)_2CH_2$—$C(O)R^{14}$--.
Line 56, "5. —N—$CH(CH(CH_3)_2))$—$C(O)R^{14}$" should read
--5. —N—$CH(CH(CH_3)_2)$—$C(O)R^{14}$--.
Line 57, "6. —NH—$CH(CH_2(CH(CH_3)_2)))$—$C(O)R^{14}$" should read
--6. —NH—$CH(CH_2(CH(CH_3)_2))$—$C(O)R^{14}$--.

Column 149,
Lines 33-34, "early stages diabetes" should read --early stage diabetes--.

Column 150,
Line 15, "Insulin/Insulin Analozues" should read --Insulin/Insulin Analogues--.

Column 152,
Line 60, "Wiemsperger" should read --Wiernsperger--.

Column 158,
Line 56, "CP-9971 1" should read --CP-99711--.

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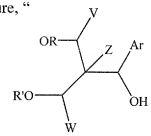
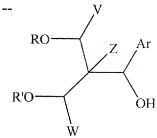
Column 160,
Line 46, "Foley T E" should read --Foley J E--.

Column 170,
Line 32, "oxidation of one the" should read --oxidation of one of the--.

Columns 171-172,
Bottom center figure, " 

" should read -- 

--.

Column 174,
Line 33, "alkylarninocarbonyl" should read --alkylaminocarbonyl--.

Column 177,
Line 32, "(Dom et al," should read --(Dorn et al,--.

Column 179,
Line 63, "synthesis of f tiran" should read --synthesis of furan--.

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Column 181,
Linc 34, "wherein G=S" should read --wherein G"=S--.

Column 182,
Line 3, "can made in" should read --can be made in--.
Line 36, "reactions in presence of" should read --reactions in the presence of--.

Column 186,
Lines 9-10, "are each optionally is a carboxamido" should read
--are each optionally a carboxamido--.
Lines 21-22, "are each optionally is an" should read --are cach optionally an--.

Column 192,
Lines 17-18, "(1.1 n unolc)" should read --(1.1 mmole)--.

Column 194,
Line 36, "N: 5.5" should read --N: 5.53--.

Column 195,
Lincs 34-35, "(3.27) 2-Amino-5-cyclopropyl-4-[2-(5-phosphono)fi aranyl]thiazole."
should read --(3.27) 2-Amino-5-cyclopropyl-4-[2-(5-phosphono)furanyl]thiazole.--
Line 60, "(3.33) ^{2}-Amino-" should read --(3.33) 2-Amino- --.

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 196,
Line 1, "(3.35) ^{2}-Amino-" should read --(3.35) 2-Amino- --.
Line 5, "(3.36) ^{2}-Amino-" should read --(3.36) 2-Amino- --.
Line 20, "(3.40) ^{2}-Amino-" should read --(3.40) 2-Amino- --.
Line 27, "(3.42) ^{2}-Methyl-" should read --(3.42) 2-Methyl- --.
Line 28, "$C_{11/l12}NO_4PS+0.3$" should read --$C_{11}H_{12}NO_4PS+0.3$--.

Column 197,
Line 48, "(3.67) ^{2}-Amino-" should read --(3.67) 2-Amino- --.

Column 199,
Line 50, "(3 m mole)" should read --(3 mmole)--.

Column 200,
Line 6, "N: 10.21." should read --N: 11.18.--.
Lines 45-46, "(6.2) 2-Methyl-5-isopropyl-4-[2-(5-phosphorodiamido)f tiranyl]thiazole" should read --(6.2)2-Methyl-5-isopropyl-4-[2-(5-phosphorodiamido)furanyl]thiazole--.

Column 201,
Lines 47-49, "2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1 methoxycarbonyl)ethyl) phosphona mnido]- furanyl}thiazole" should read --2-amino-5-isobutyl-4-{2-[5-(O-phenyl-N-(1 methoxycarbonyl)ethyl) phosphonamido]-furanyl}thiazole--.

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 203,
Line 24, "$C_{21}H_{24}N_3O_5PS+0.2$" should read --$C_{21}H_{24}N_{30}O_5PS+0.2$--.
Lines 35-37, "(6.35) 2-amino-5-isobutyl-4-{2-[5-(4,5-benzo-1-oxo-1-phospha-2-oxa-6-6-aza)cyclo-hexan-1-yl]fi aranyl}thiazole." should read --(6.35) 2-amino-5-isobutyl-4-{2-[5-(4,5-benzo-1-oxo-1-phospha-2-oxa-6-6-aza)cyclo-hexan-1-yl]furanyl}thiazole.--.
Line 50, "A solution of AlC_{13}" should read --A solution of $AlCl_3$--.

Column 204,
Line 1, "with CH_2C_{12}" should read --with CH_2Cl_2--.

Column 207,
Lines 24-25, "C: 52.26; 7.06; 10.60. Found: C: 52.21; 6.93; 10.62." should read --C: 52.26; H: 7.06; N: 10.60. Found: C: 52.21; H: 6.93; N: 10.62.--.
Line 32, "C_{35} H_{45} N_4 O_6 P S+0.5" should read --C_{35} H_{45} N_4 O_6 P S+0.5--.
Line 47, "P S3: C:" should read --P S_3: C:--.
Line 56, "H: 6.97; H: 7.90. Found: C: 62.85; h 7.06, 7.81." should read --H: 6.97; N: 7.90. Found: C: 62.85; H: 7.06, N: 7.81.--

Column 208,
Lines 2-3, "H: 8.42. Found: C: 59.88; H: 6.28; H: 8.32." should read --N: 8.42. Found: C: 59.88; H: 6.28; N: 8.32.--.
Line 8, "H: 8.98." should read --N: 8.98.--.
Line 39, "bis-phosphoroarnidate" should read --bis-phosphoroamidate--.

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 209,
Line 35, "N_3-methyl-2-iodobenzene-1-sulfonamide" should read
--N^1-methyl-2-iodobenzene-1-sulfonamide--.
Lines 40-42, "N^1-(4-5 chlorobenzyl)-2-iodobenzamide (for 13.14); Nl-(4-chlorophenethyl)-2-iodobenzamide (for 13.15); N1-benzyl-2-iodobenzene-1-sulfonamide" should read
--N^1-(4-chlorobenzyl)-2-iodobenzamide (for 13.14); N^1-(4-chlorophenethyl)-2-iodobenzamide (for 13.15); N^1-benzyl-2-iodobenzene-1-sulfonamide--.

Column 209,
Line 51, "N1-(2,4-difluorophenyl)-2-iodobenzamide" should read
--N^1-(2,4-difluorophenyl)-2-iodobenzamide--.
Line 55, "(for 15 13.31);" should read --(for 13.31);--.
Lines 63-64, "N1-(4-iodophenyl)-2-tetrahydro-1H-pyrrol-1-ylacetamide" should read
--N^1-(4-iodophenyl)-2-tetrahydro-1H-pyrrol-1-ylacetamide--.

Column 210,
Line 28, "(1m mol)" should read --(1 mmol)--.

Column 213,
Line 42, "2 MM" should read --2 mM--.

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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 214,
Line 47, "Vervoom" should read --Vervoorn--.

Column 216,
Line 28, "5-bromo-1-μD-ribofuranosyl-imidazole-carboxamide" should read --5-bromo-1-βD-ribofuranosyl-imidazole-carboxamide--.

Column 220,
Line 49, "though" should read --through--.

Column 224,
Line 25, "4 treatments groups" should read --4 treatment groups--.

Column 244,
Line 50, "R1 is" should read --R^1 is--.
Line 53, "B" is a C^1-C^6 alkyl" should read --B" is a C_1-C_6 alkyl--.
Lines 60-61, "a C1-C6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; and YR1 is OH." should read --a C_1-C_6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; and YR^1 is OH.--.
Lines 63-64, "C1-C6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R1 is" should read --C_1-C_6 alkyl or C(O)R^{11}, wherein R^{11} is alkyl; Y is NR^6 and R^6 is H; and R^1 is--.

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Column 245,
Line 2, "and R1 is" should read --and R^1 is--.
Line 7, "B" is a C1-C6" should read --B" is a C_1-C_6--.
Line 14, "is a C1-C6" should read --is a C_1-C_6--.
Lines 16-17, "and R1 is" should read --and R^1 is--.

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